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## Supplemental Figures

Figure S1. Composite plot of Study 101 SEP-363856 plasma concentration vs time.

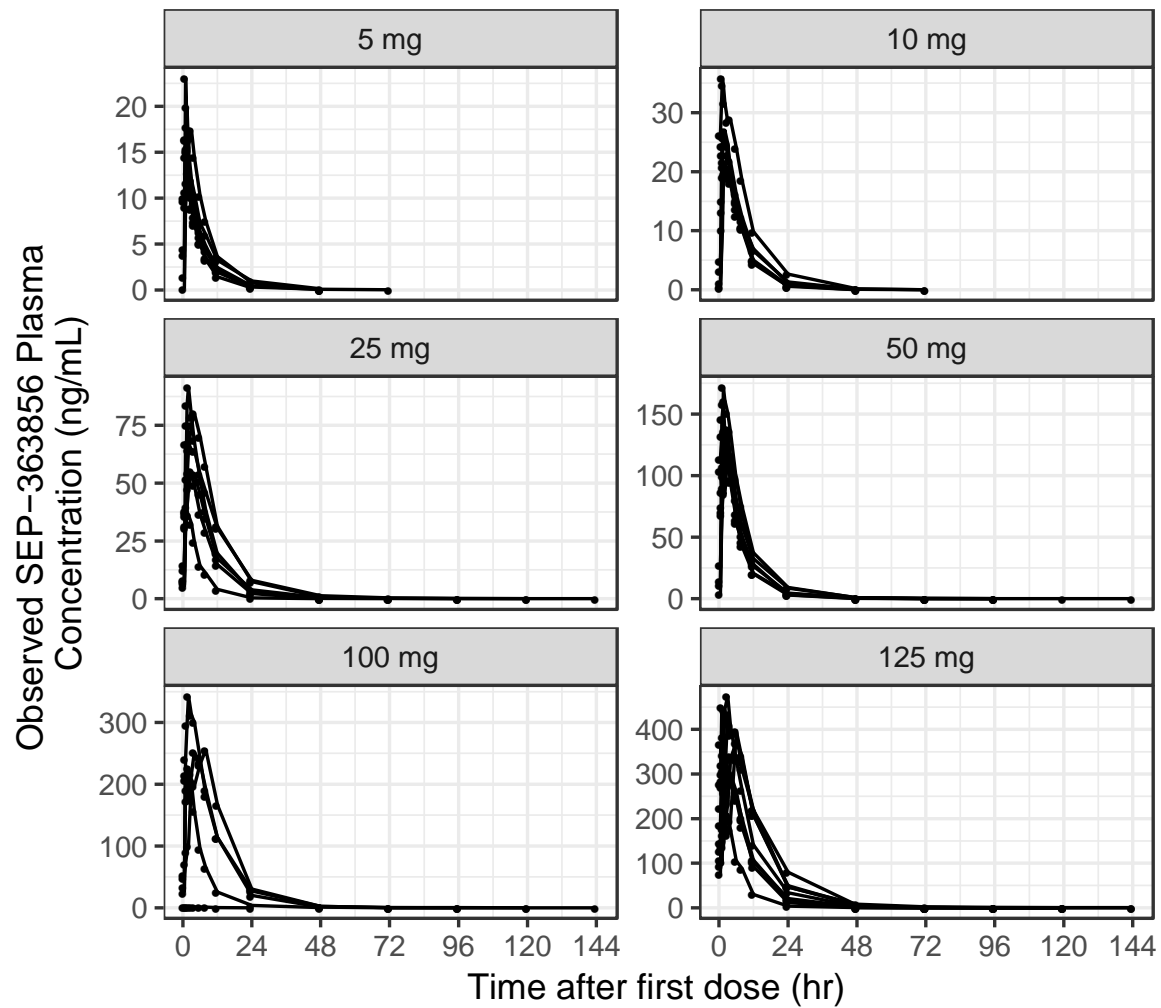


Figure S2. Composite plot of Study 103 SEP-363856 plasma concentration vs. time.

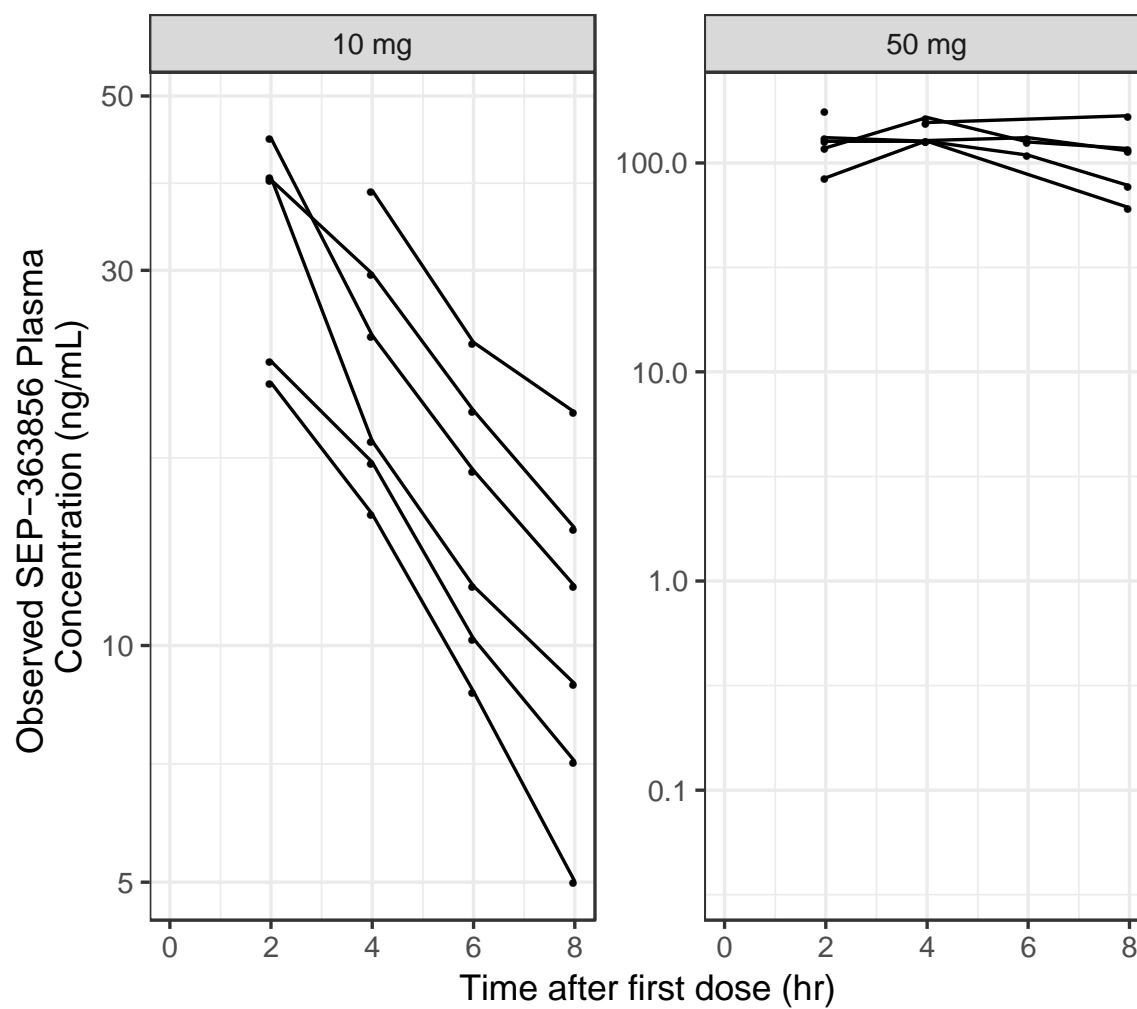


Figure S3. Composite plot of Study 105 SEP-363856 plasma concentration vs. time.

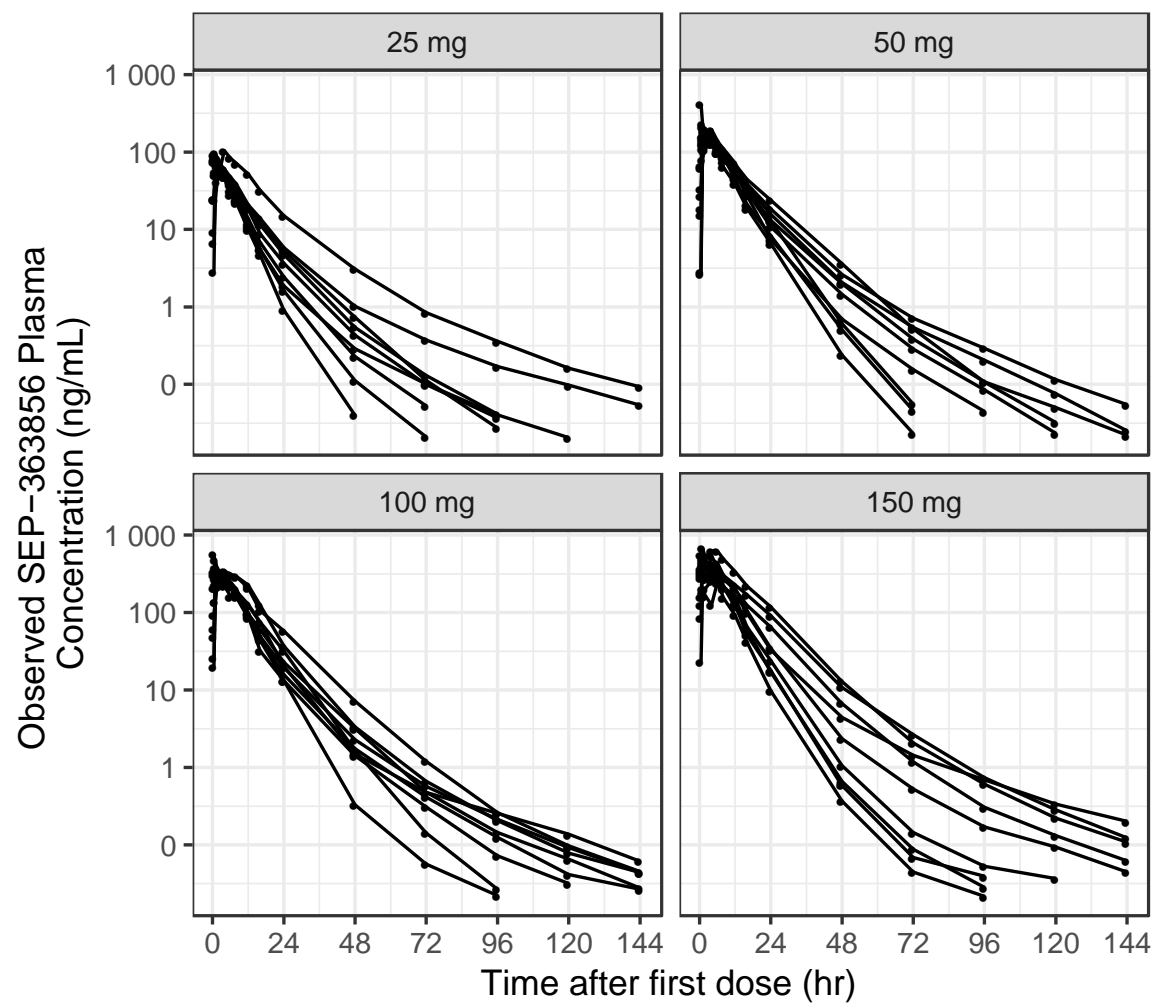


Figure S4. Composite plot of Study 106, Part 1 SEP-363856 plasma concentration vs. time.

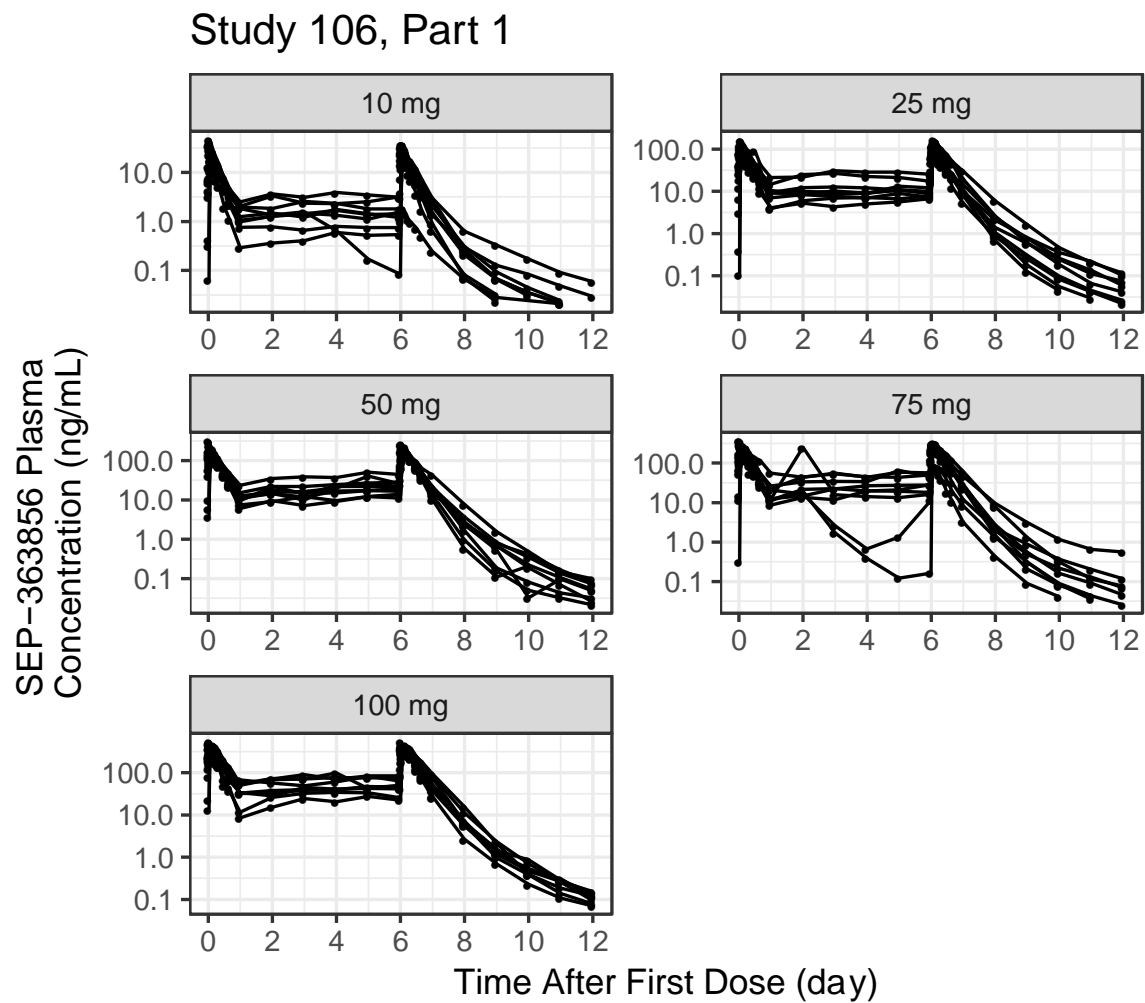


Figure S5. Composite plot of Study 106, Part 2 SEP-363856 plasma concentration vs. time following 75 mg QD dosing.

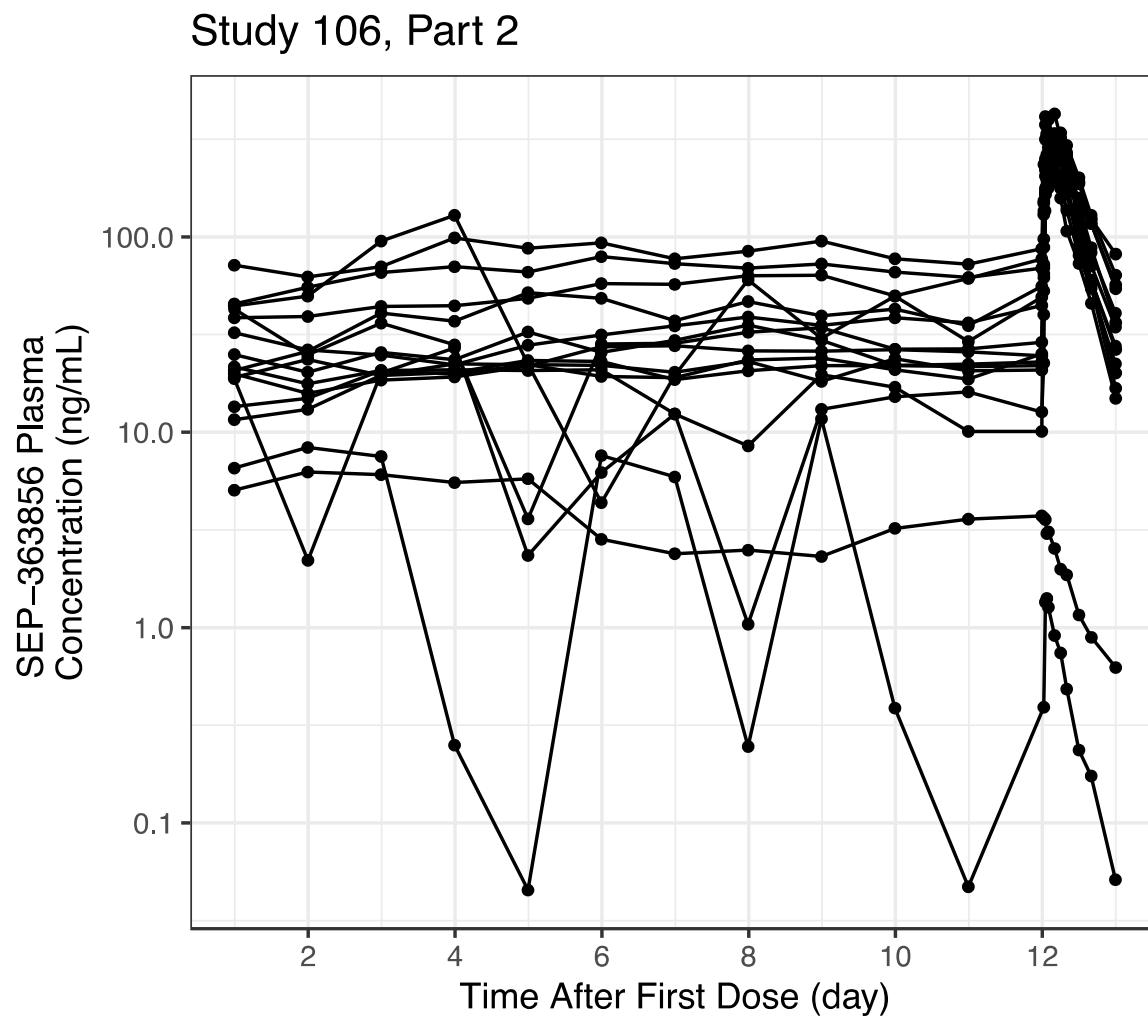


Figure S6. Composite plot of Study 111 SEP-363856 plasma concentration vs. time.

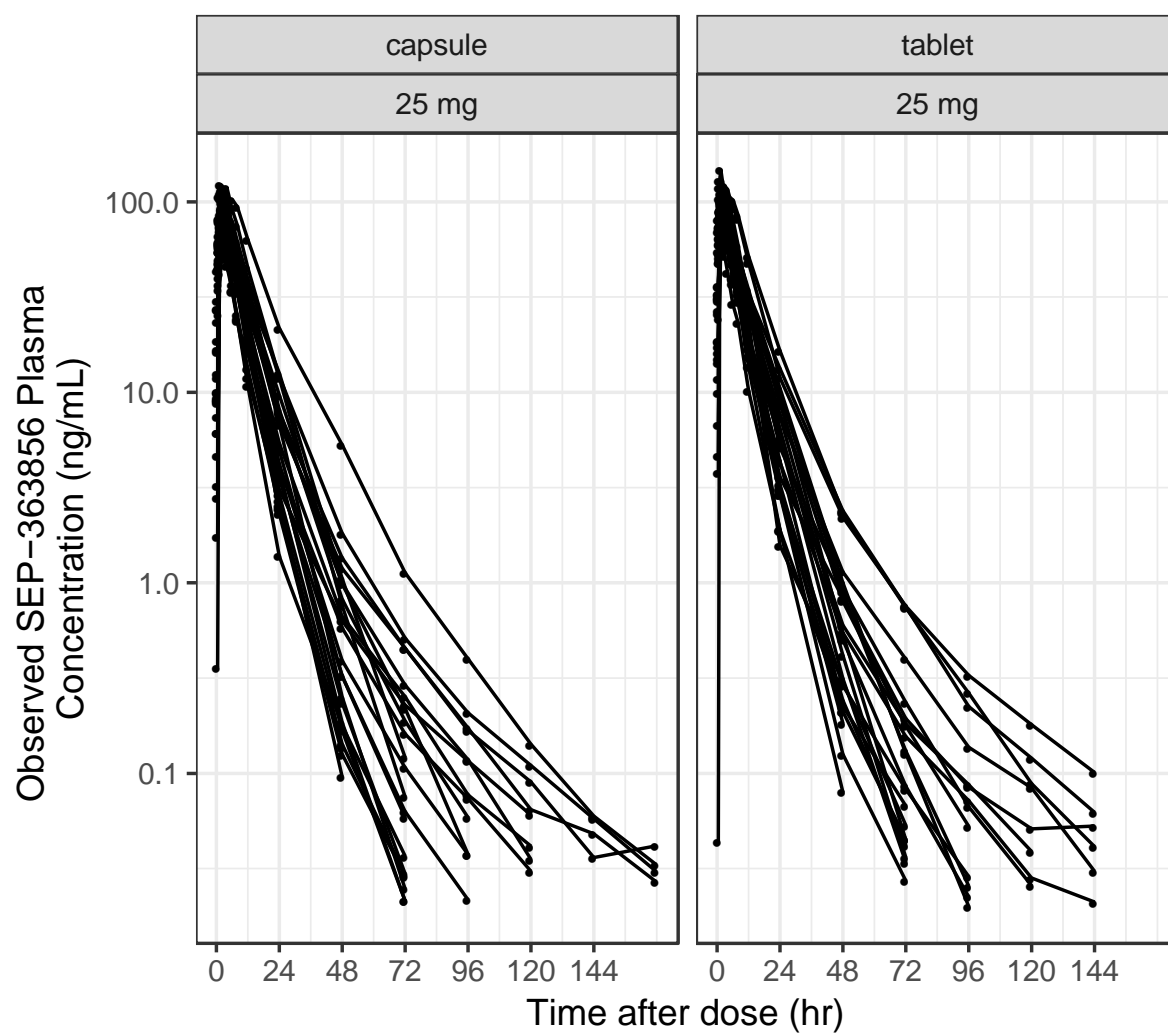


Figure S7. Composite plot of Study 801002 SEP-363856 plasma concentration vs. time.

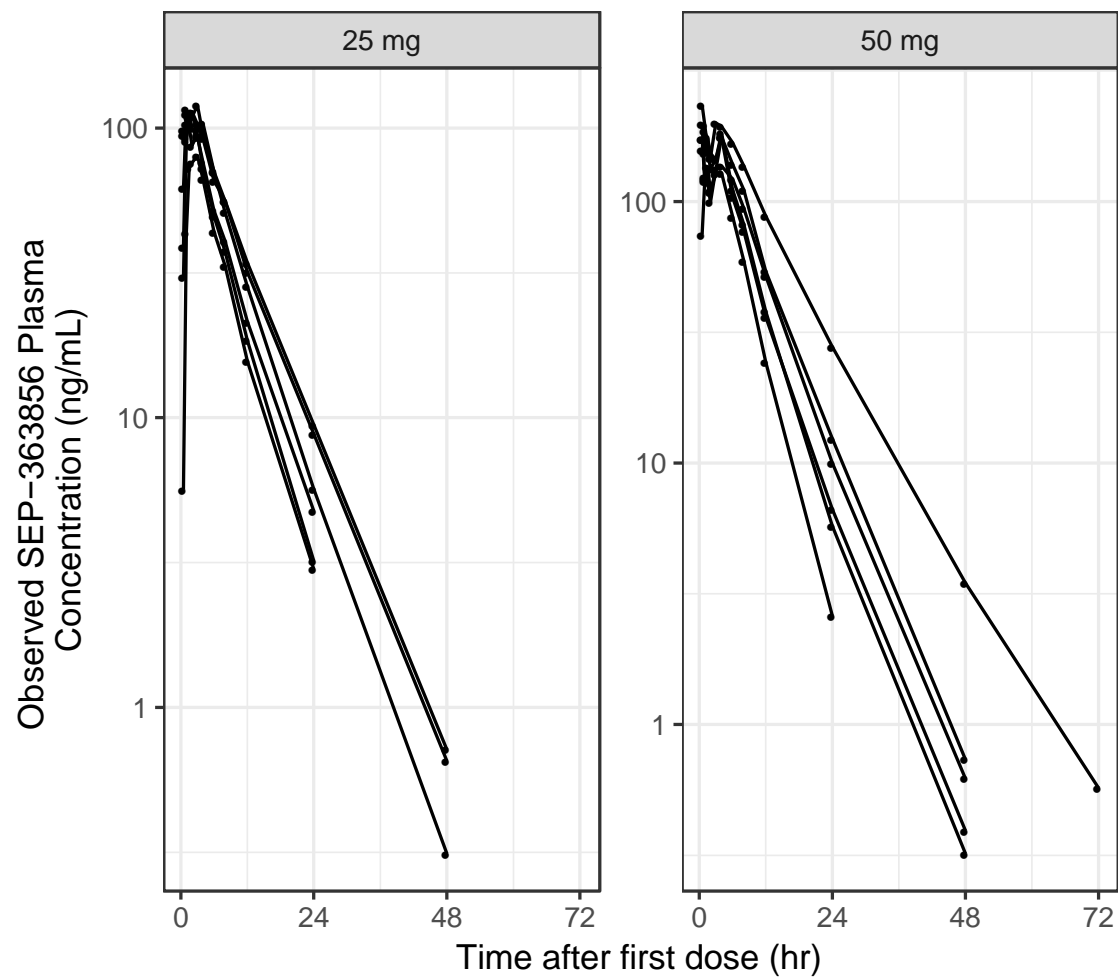
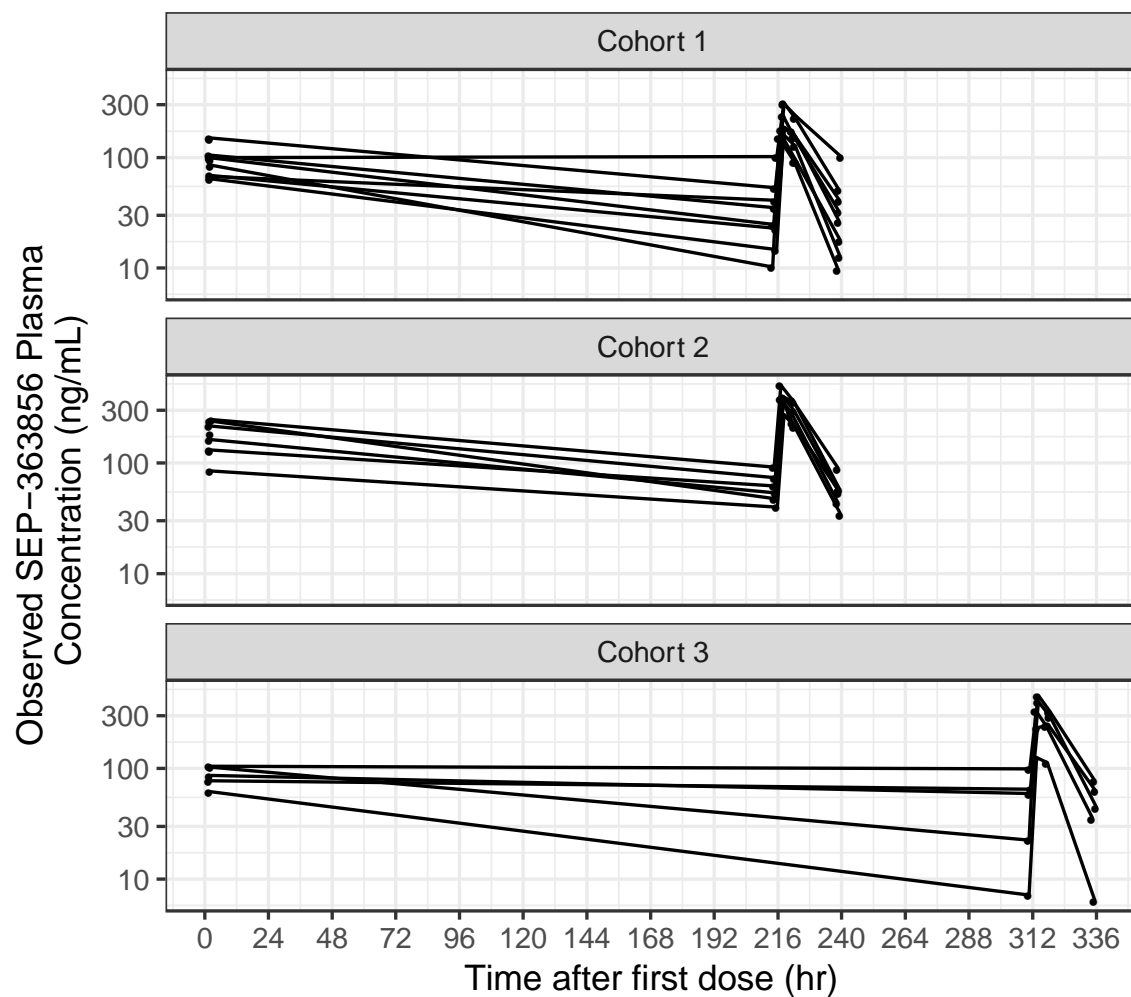


Figure S8. Composite Plot of Study 1004 SEP-363856 plasma concentration vs. time by cohort<sup>1</sup>.



<sup>1</sup> Cohort 1 received 3 days of 25 mg QD followed by 3 days of 50 mg QD, cohort 2 received 50 mg QD for 3 days and then 75 mg QD for 7 days, and cohort 3 received 25 mg QD for 3 days, 50 mg QD for 4 days, and then 75 mg QD for 7 days.

Figure S9. Composite plot of study 201 SEP-363856 plasma concentration vs. time after first dose.

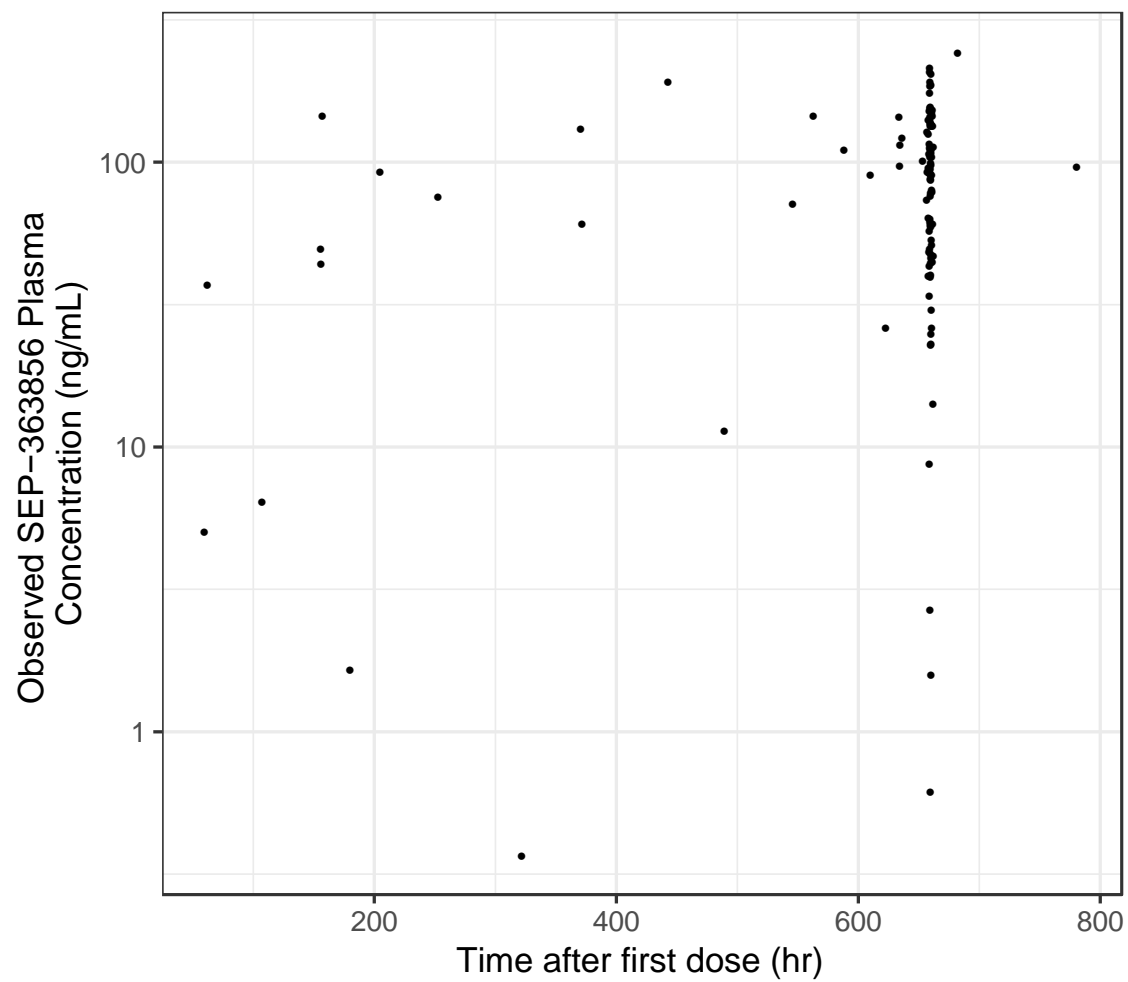


Figure S10. Composite plot of Study 201 SEP-363856 plasma concentration vs. time after dose by last administered dose.

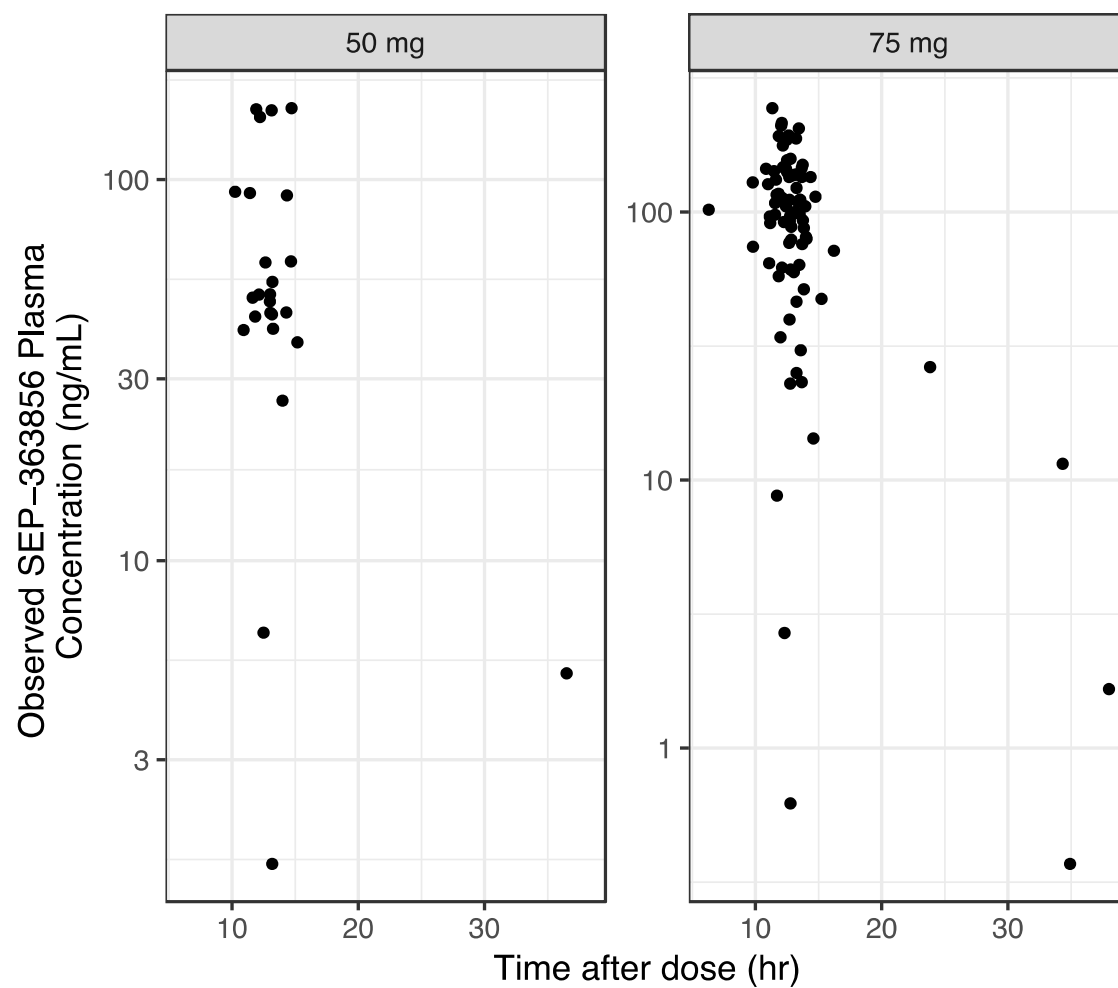


Figure S11. Composite plot of Study 202 SEP-363856 plasma concentration vs. time after first dose.

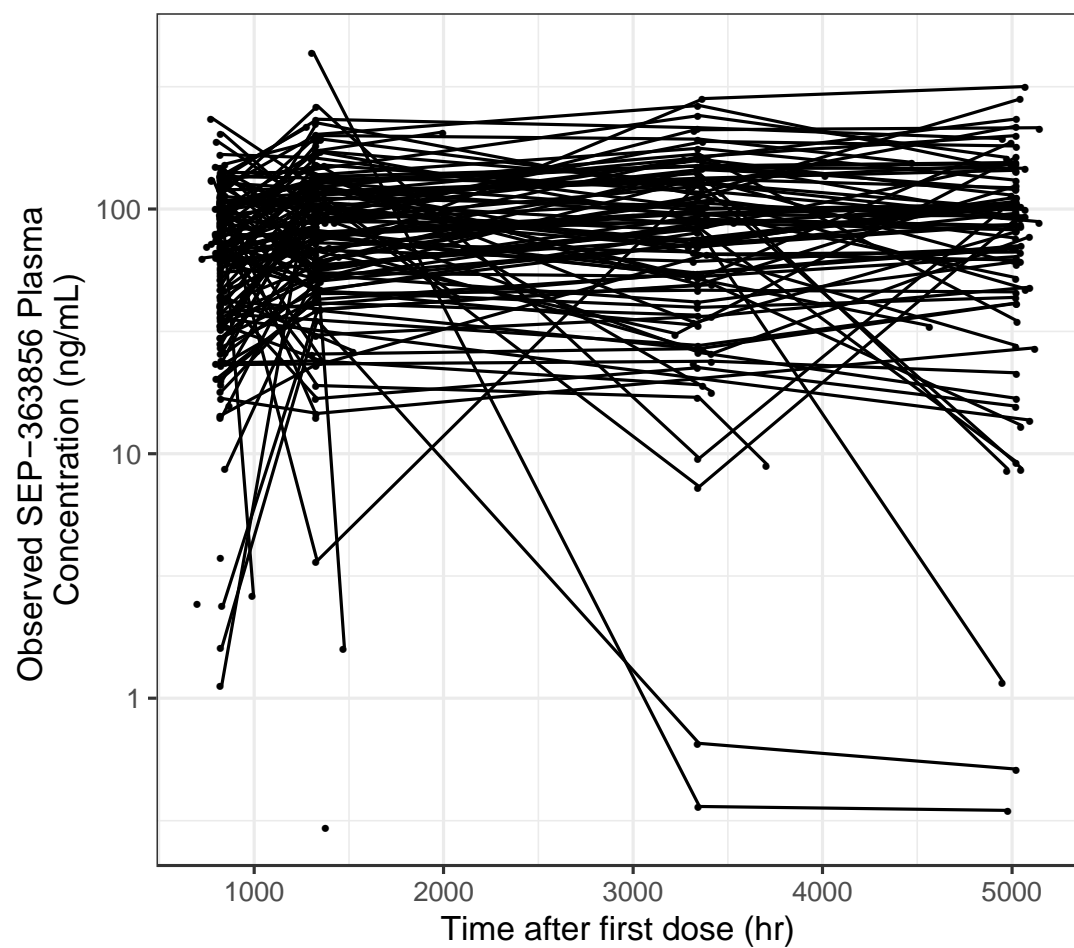
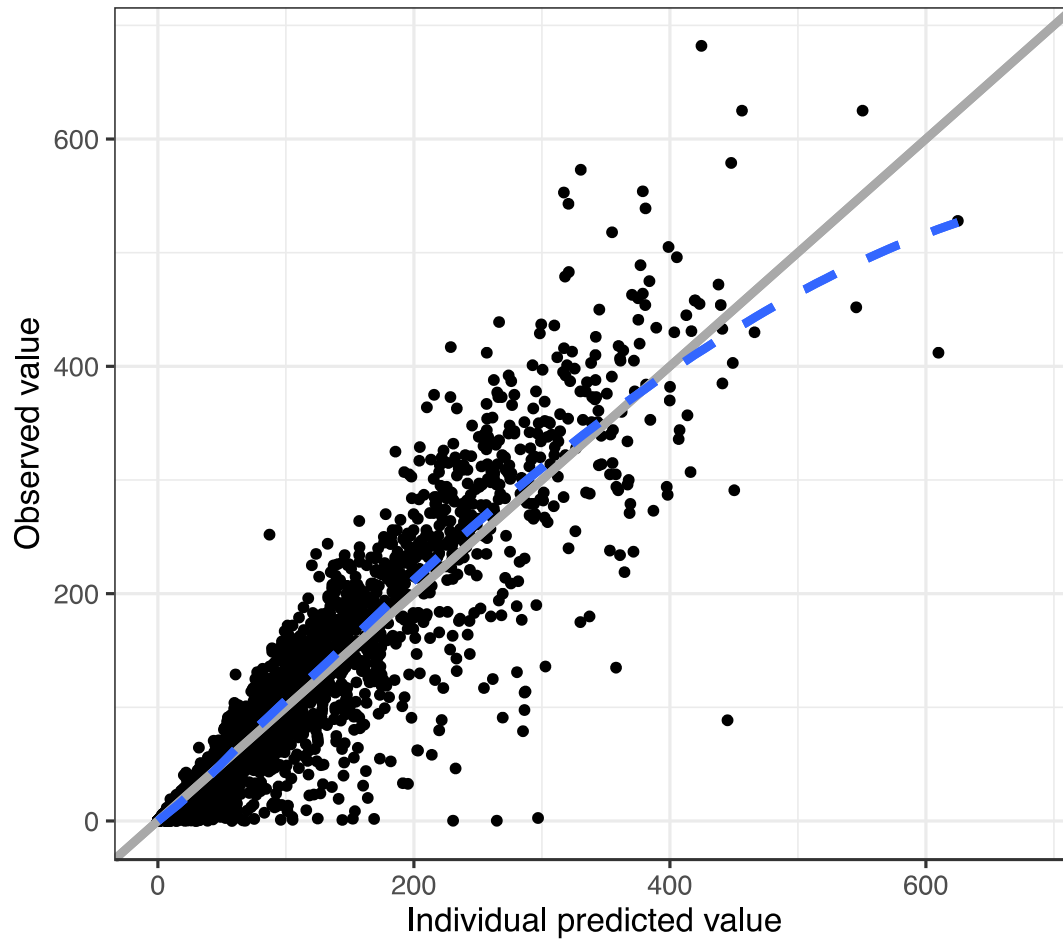
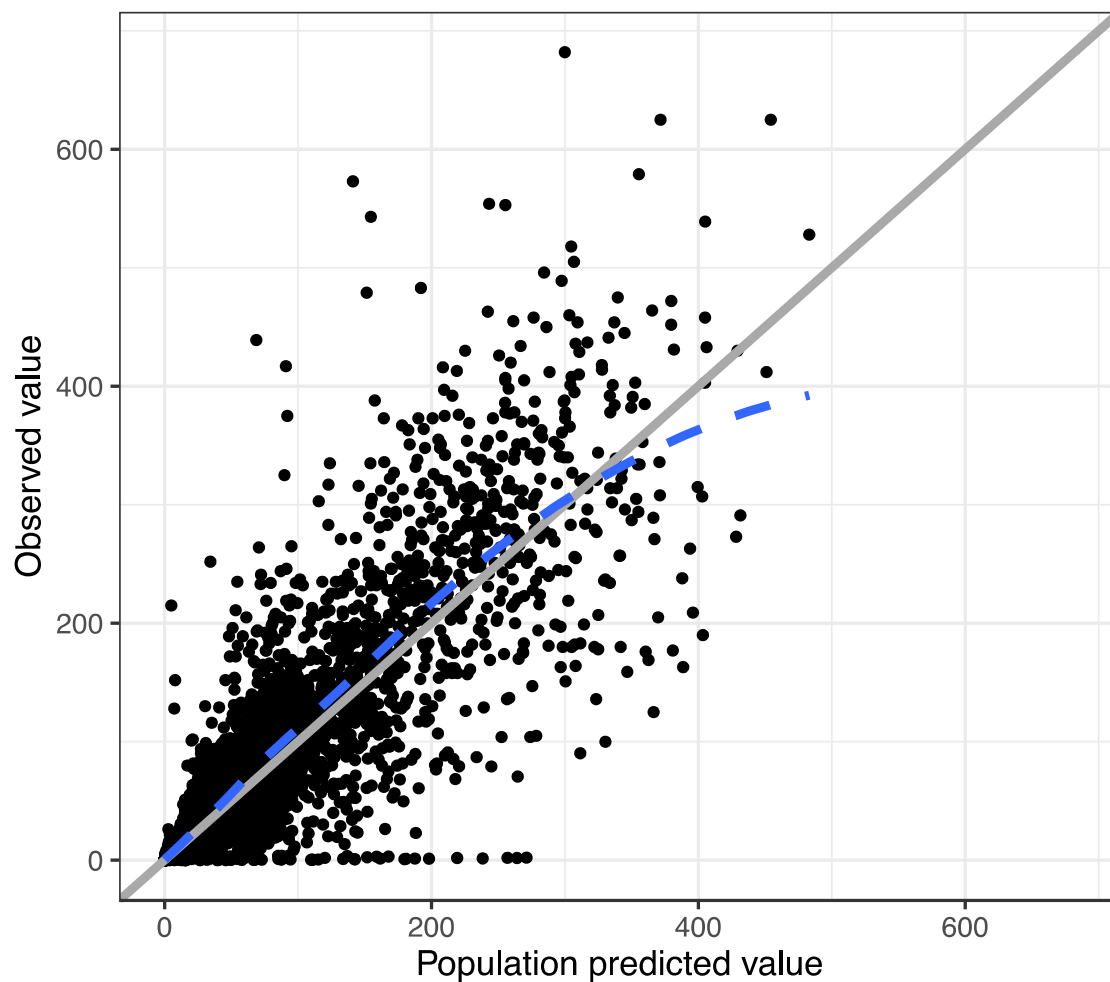


Figure S12. Observed vs individual predicted (IPRED, i.e., conditional on the random effects) values for the full model<sup>1</sup>.



<sup>1</sup> The gray line is the line of unity (predictions match observed) and the dashed blue line is a loess smooth of the points.

Figure S13. Observed vs population predicted (PRED, i.e., conditional only on patient covariates) values for the full model<sup>1</sup>.



<sup>1</sup> The gray line is the line of unity (predictions match observed) and the dashed blue line is a loess smooth of the points.

Figure S14. Weighted residuals from the full model vs time after first dose (hours).

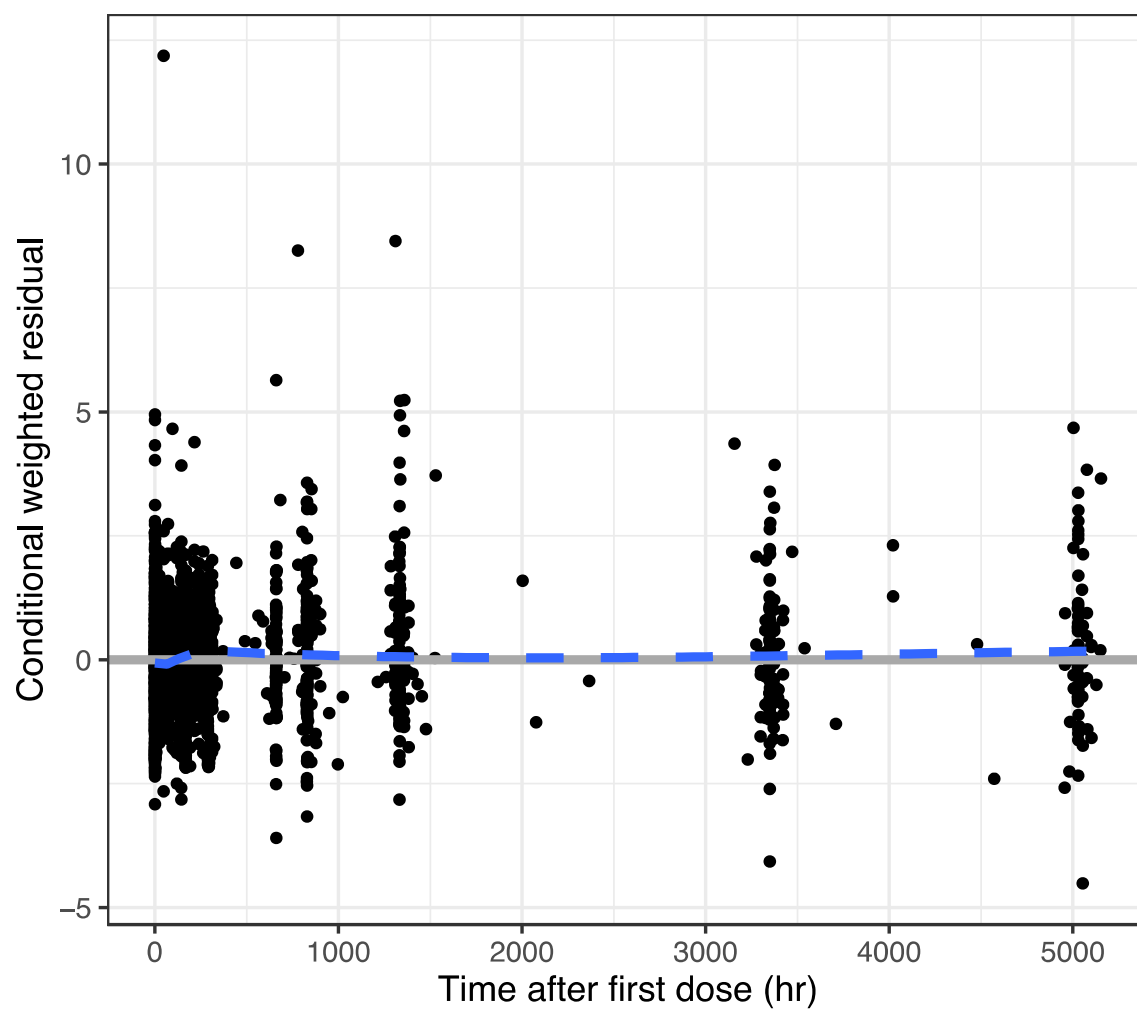


Figure S15. Weighted residuals from the full model plotted against time after dose (hours).

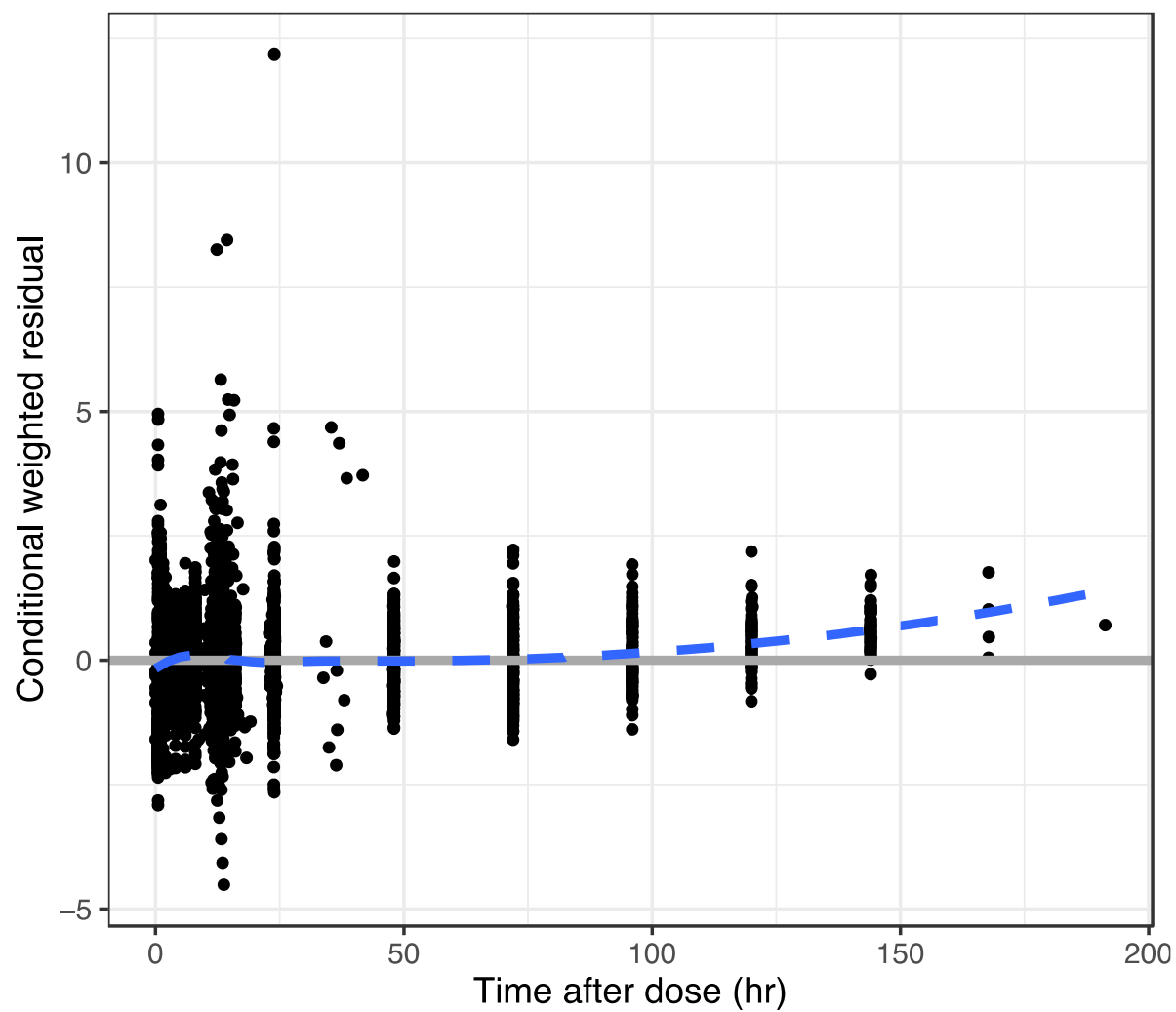


Figure S16. Weighted residuals plotted against the population predicted values (PRED) for the full model.

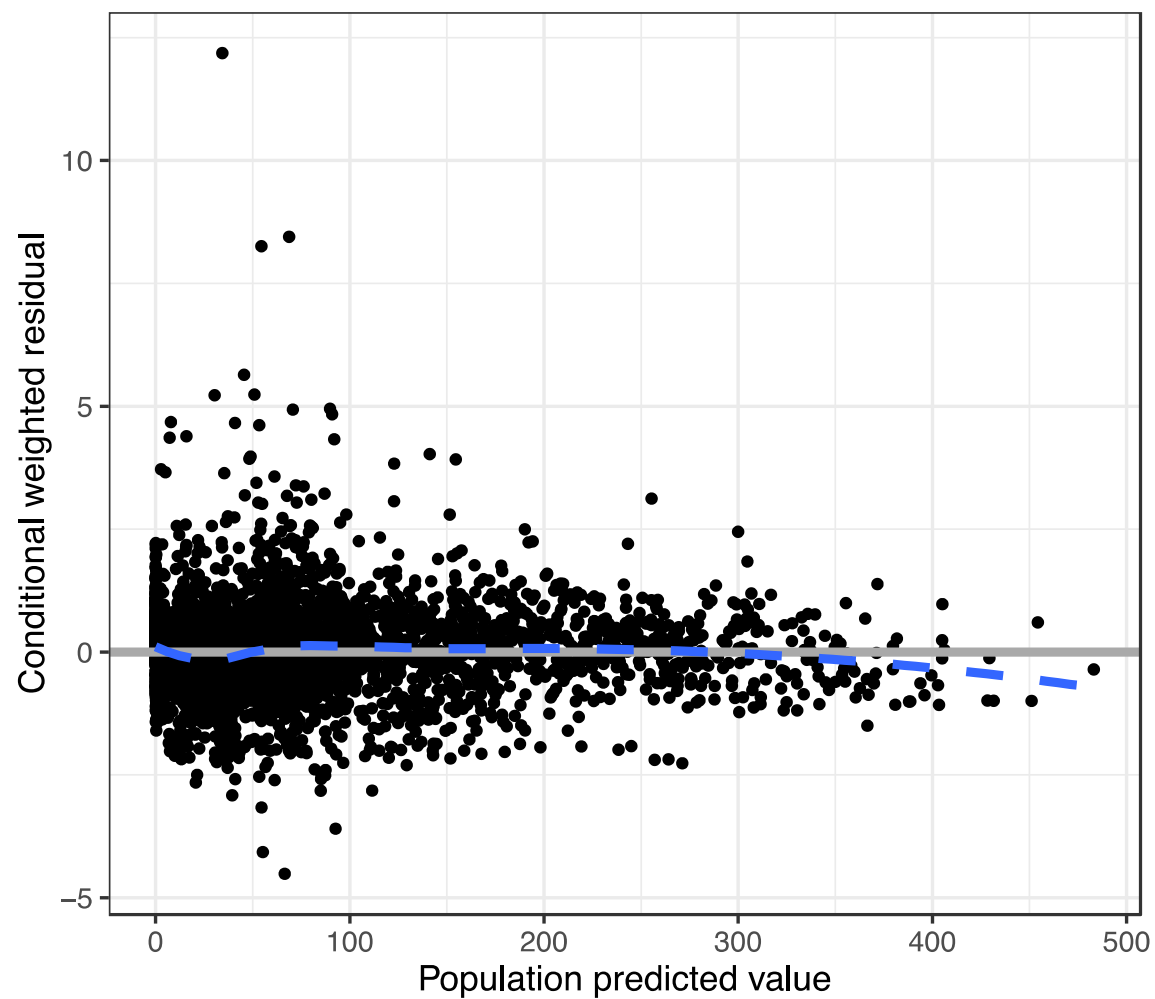
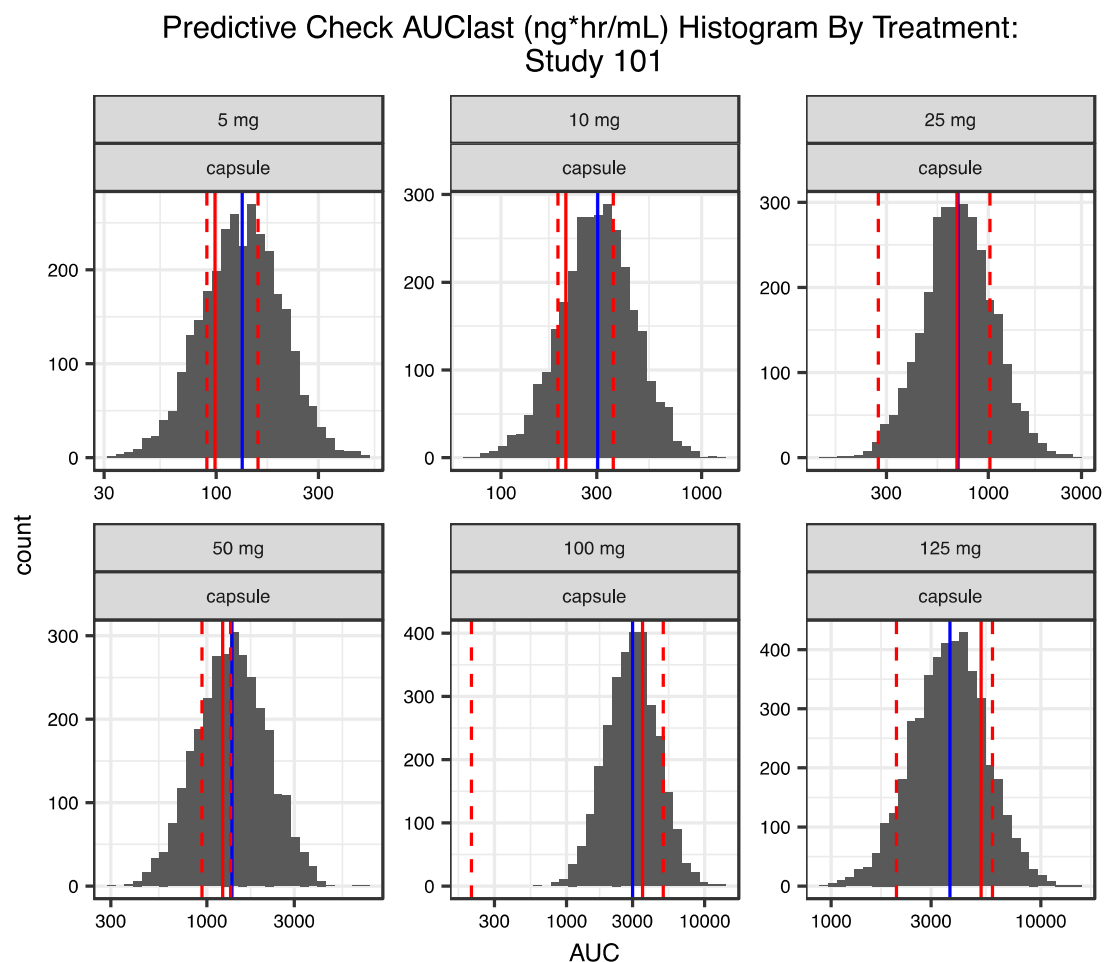
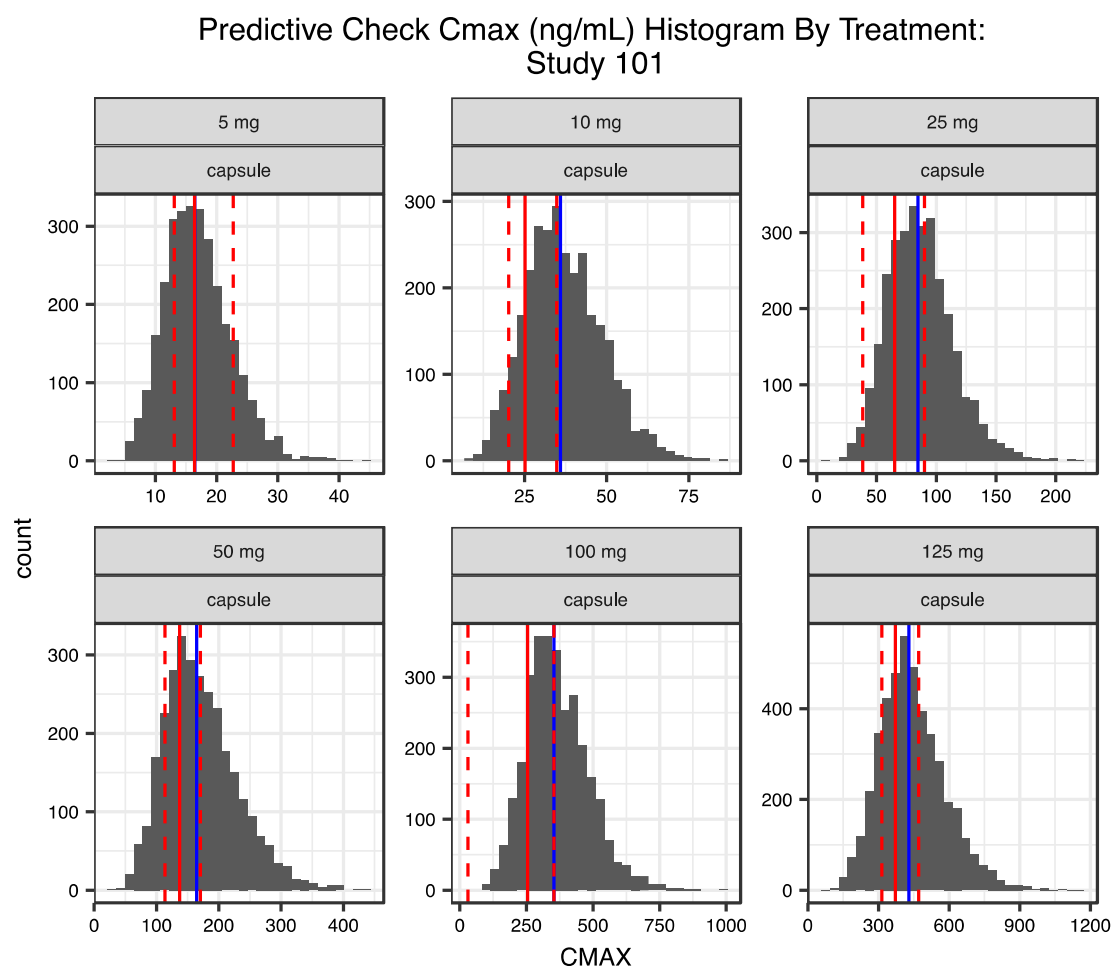


Figure S17. Predictive check for Study 101<sup>1</sup>



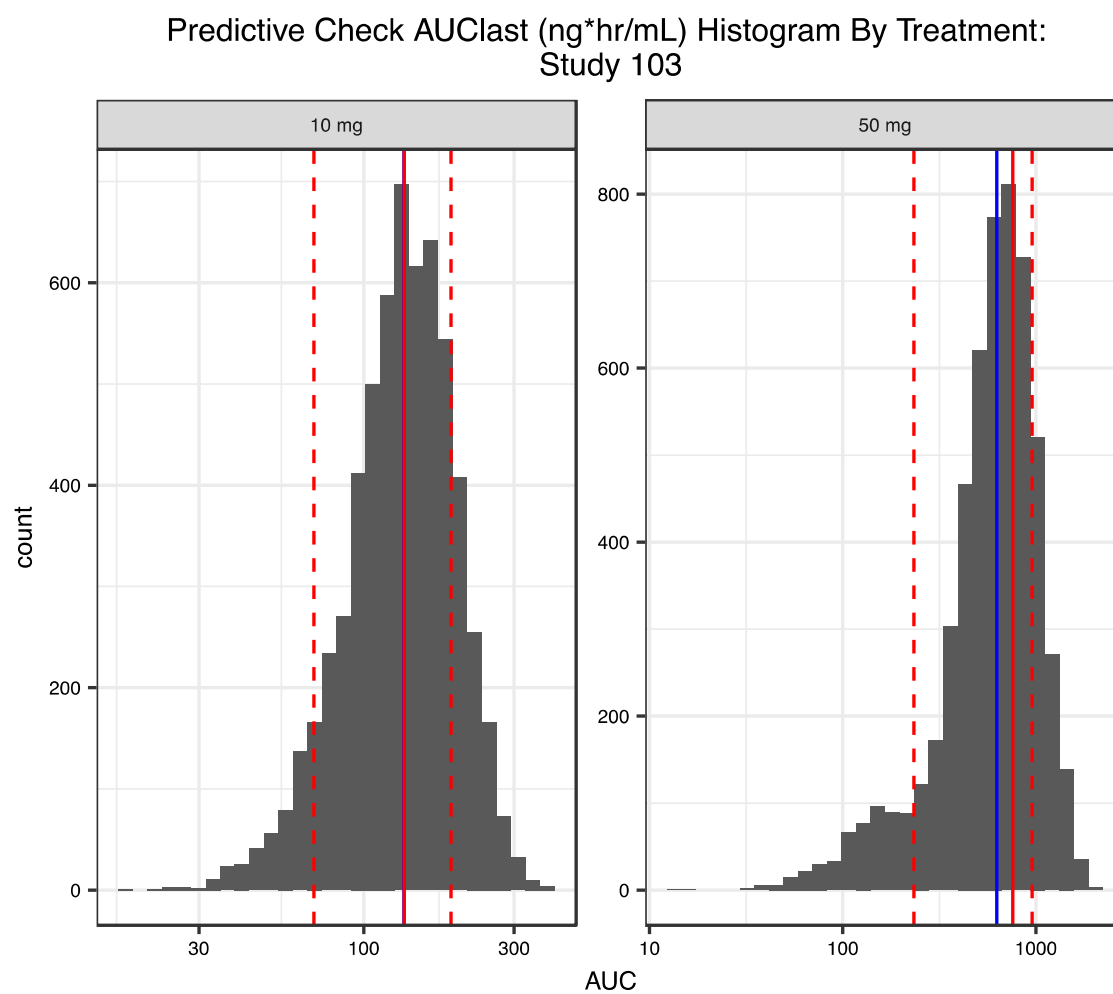
<sup>1</sup> Histograms of SEP-363856 AUCl<sub>ast</sub> values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S18. Predictive check for Study 101<sup>1</sup>.



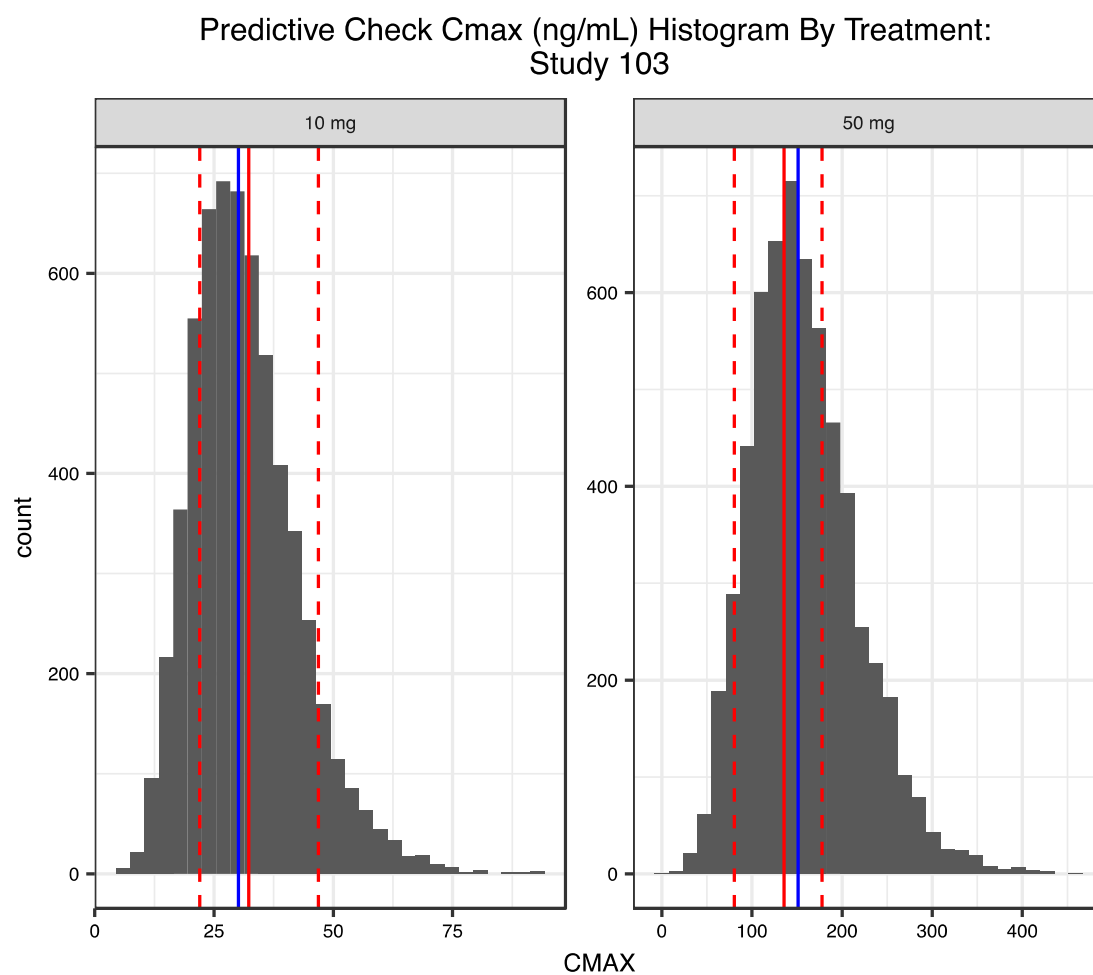
<sup>1</sup> Histograms of SEP-363856 C<sub>max</sub> values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S19. Predictive check for Study 103<sup>1</sup>.



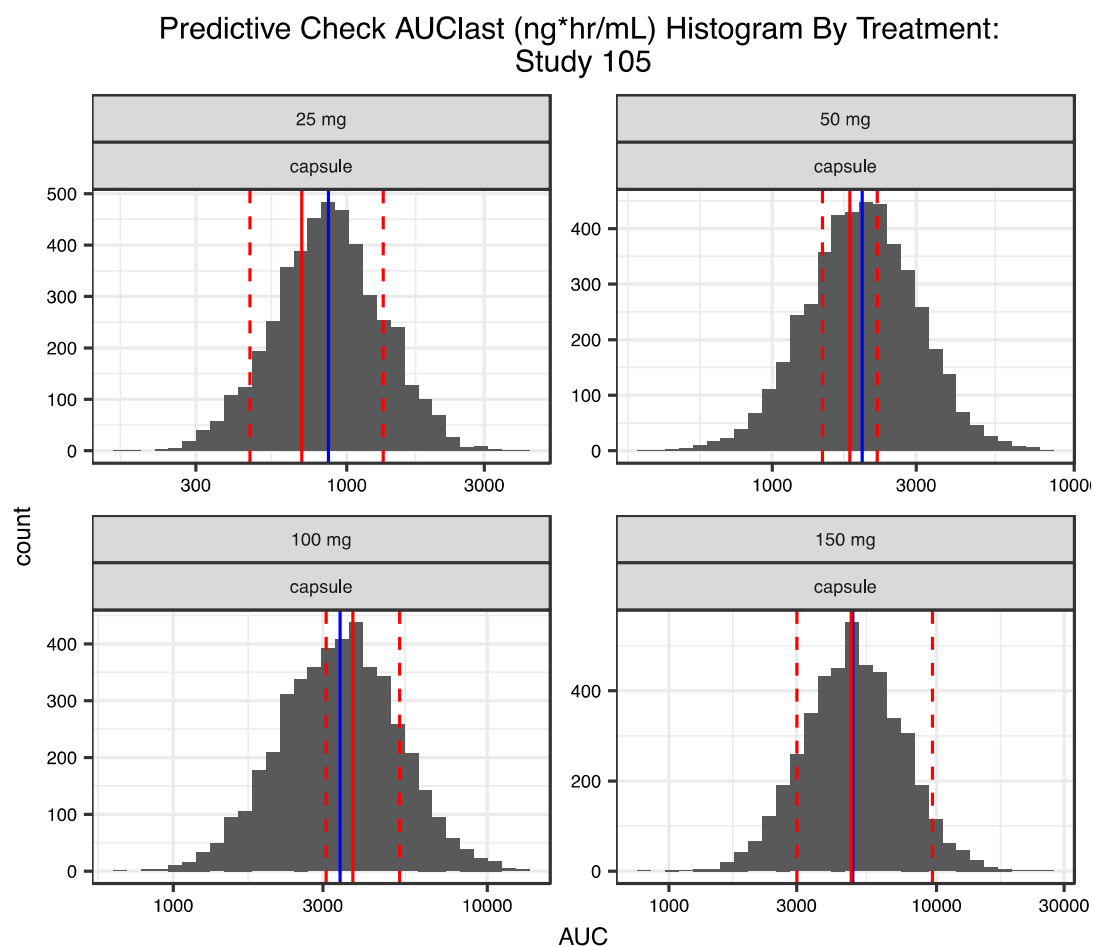
<sup>1</sup> Histograms of SEP-363856 AUC<sub>last</sub> values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S20. Predictive check for Study 103<sup>1</sup>.



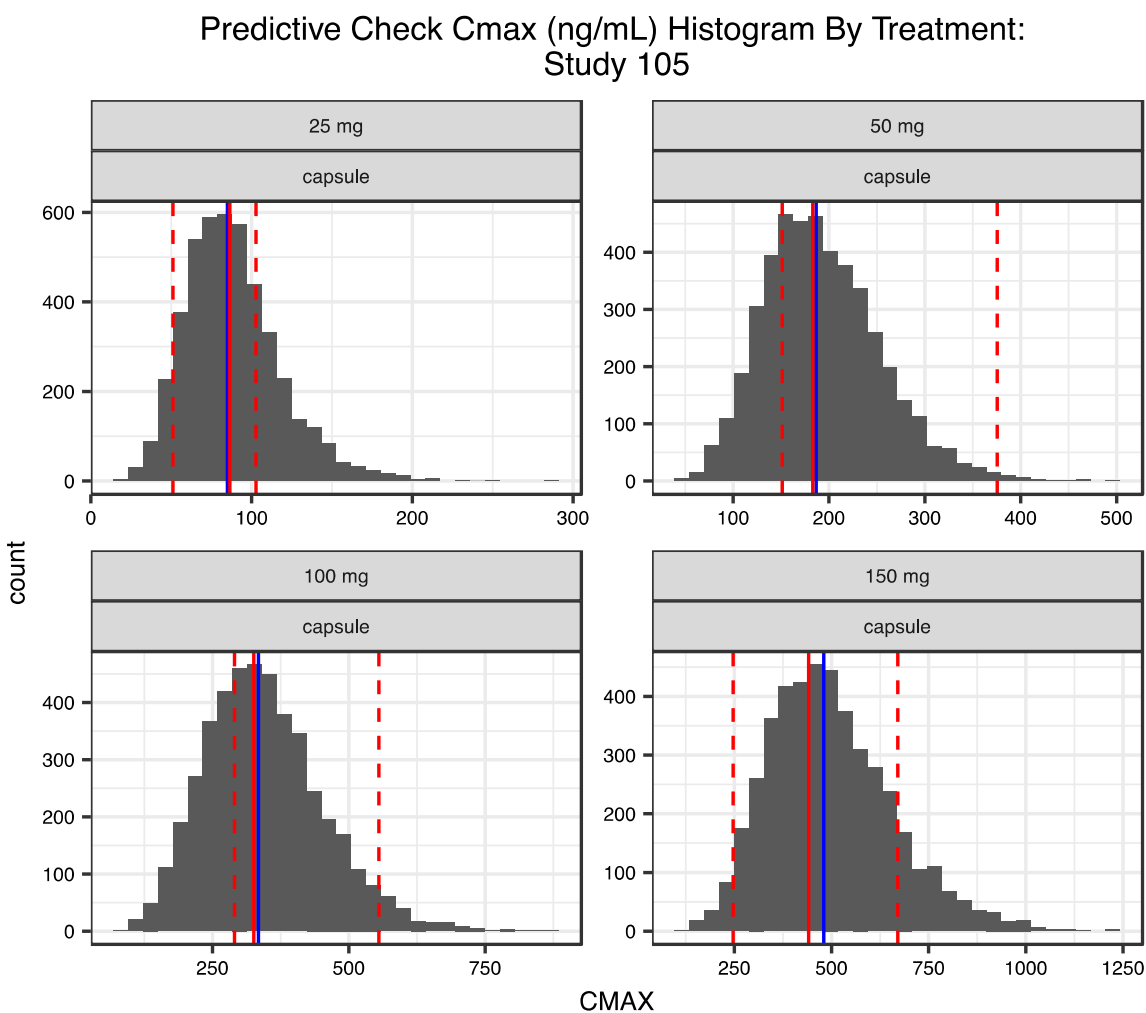
<sup>1</sup> Histograms of SEP-363856 C<sub>max</sub> values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S21. Predictive check for Study 105<sup>1</sup>.



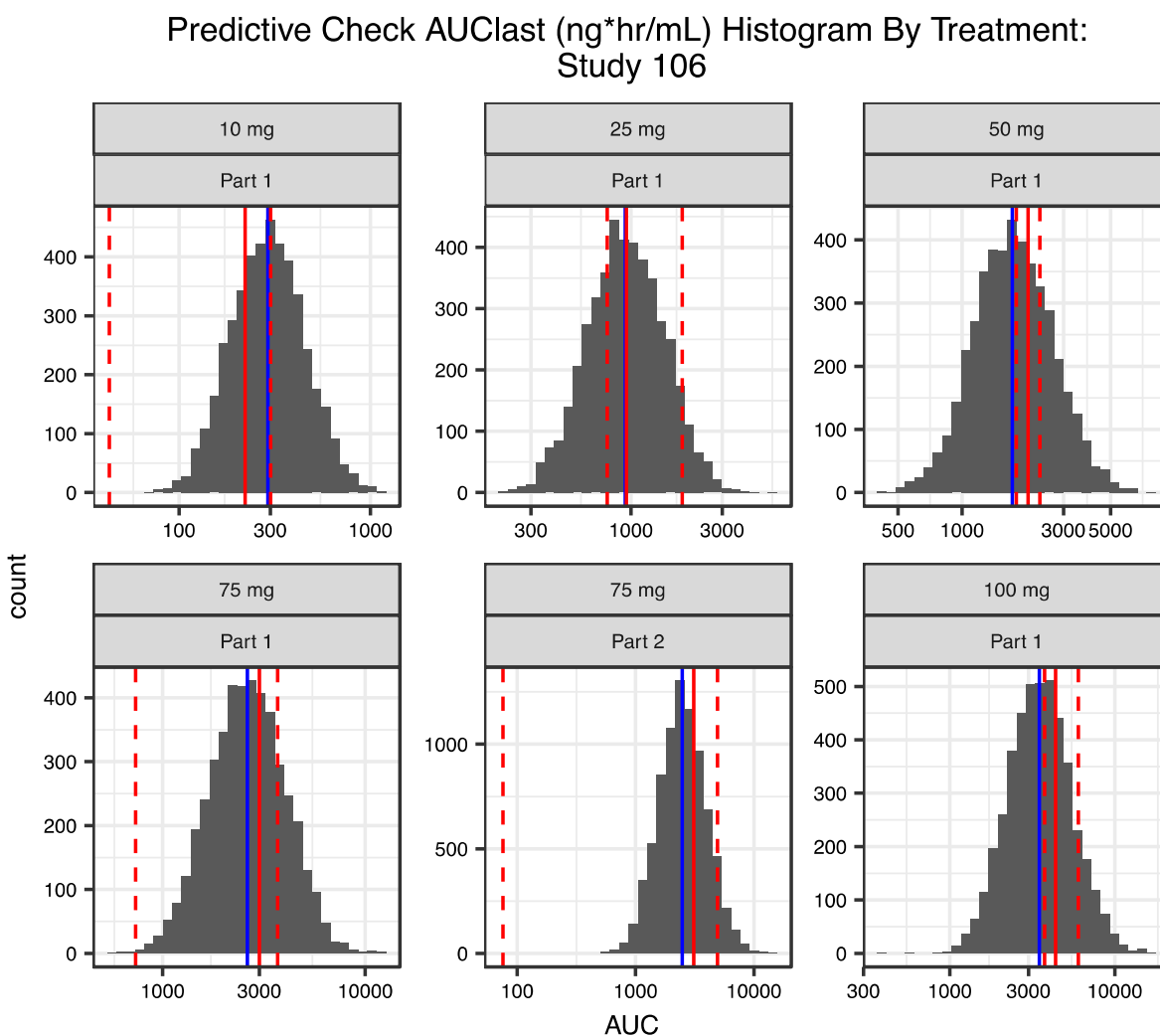
<sup>1</sup> Histograms of SEP-363856 AUCl<sub>last</sub> values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S22. Predictive check for Study 105<sup>1</sup>.



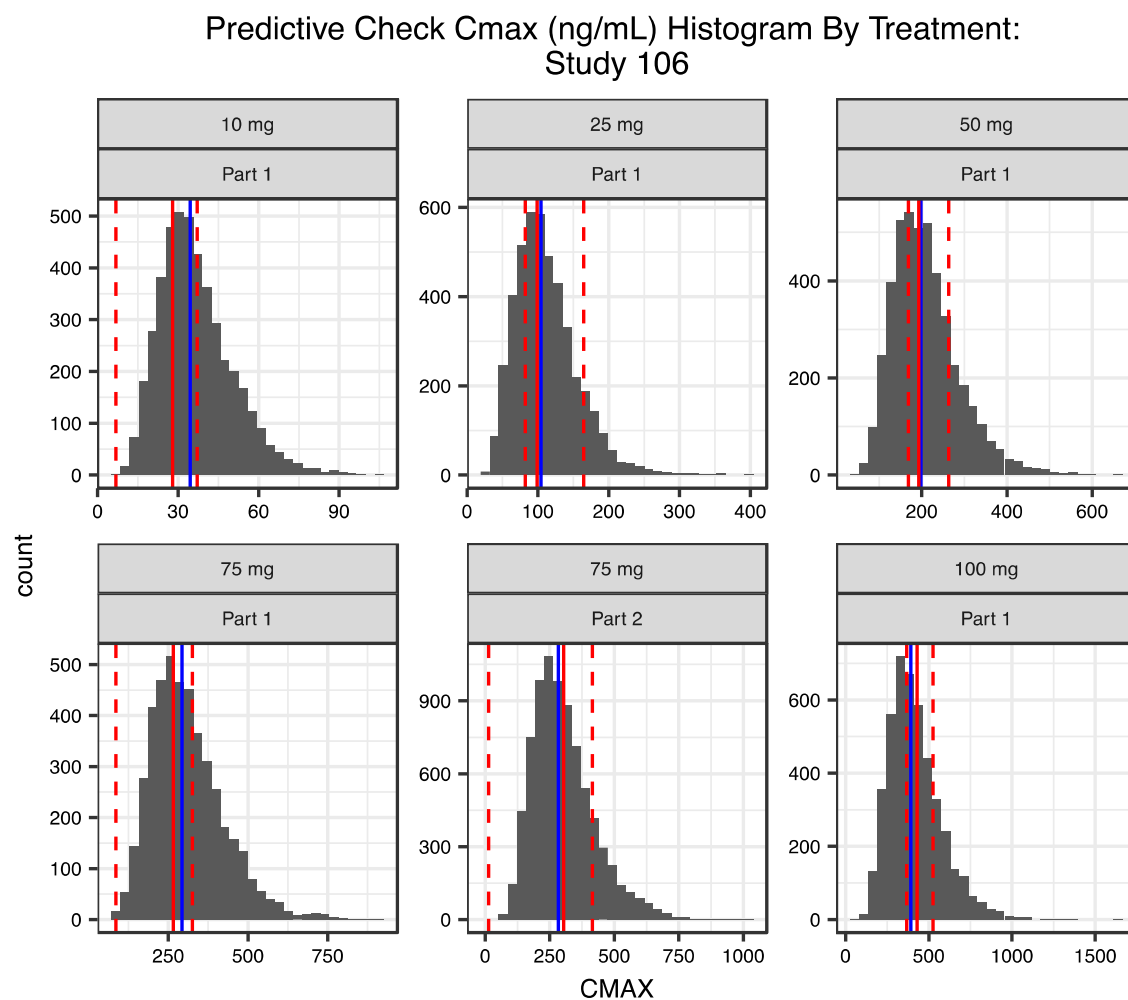
<sup>1</sup> Histograms of SEP-363856 C<sub>max</sub> values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S23. Predictive check for Study 106<sup>1</sup>.



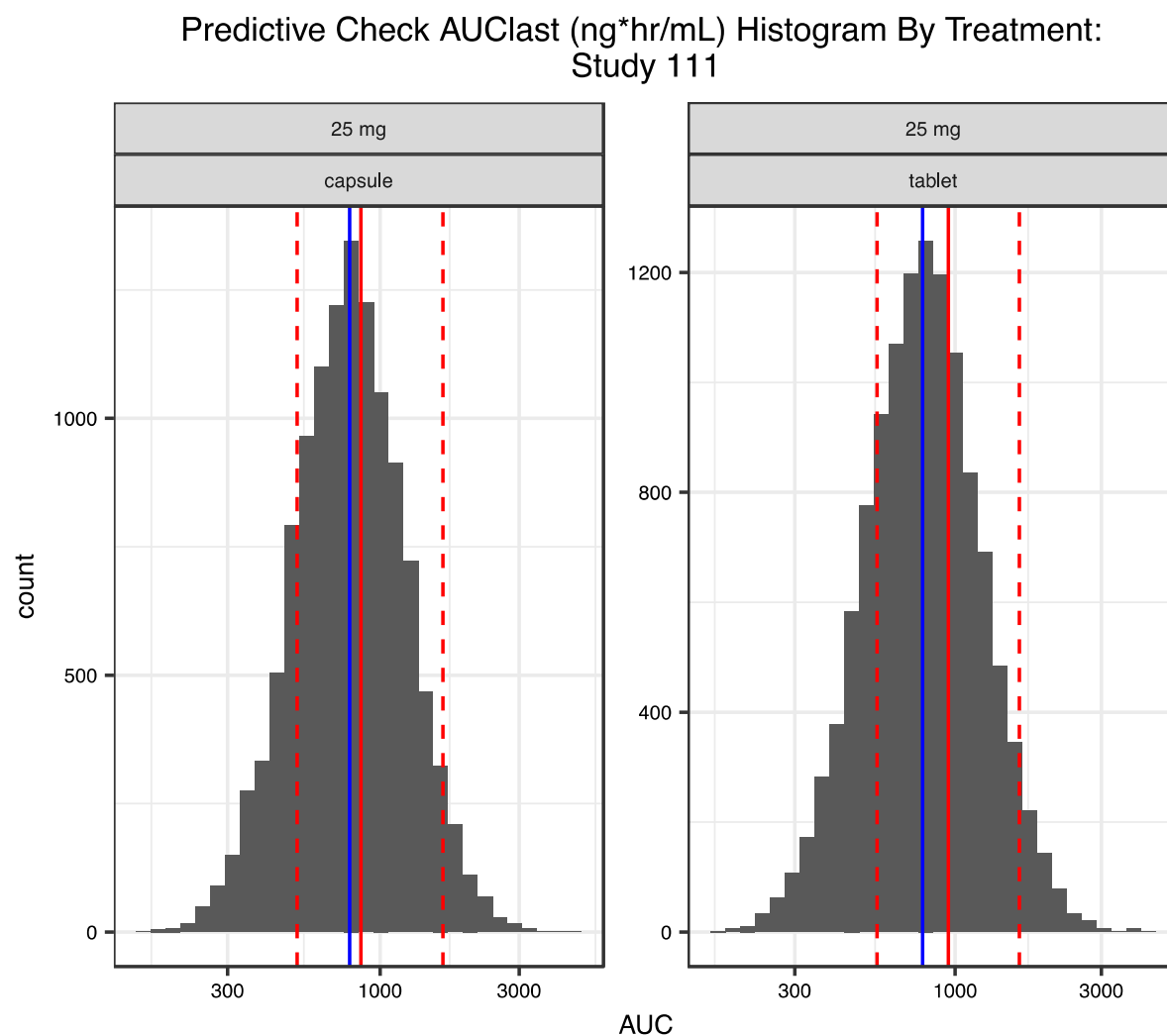
<sup>1</sup> Histograms of SEP-363856 AUC<sub>last</sub> values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S24. Predictive check for Study 106<sup>1</sup>.



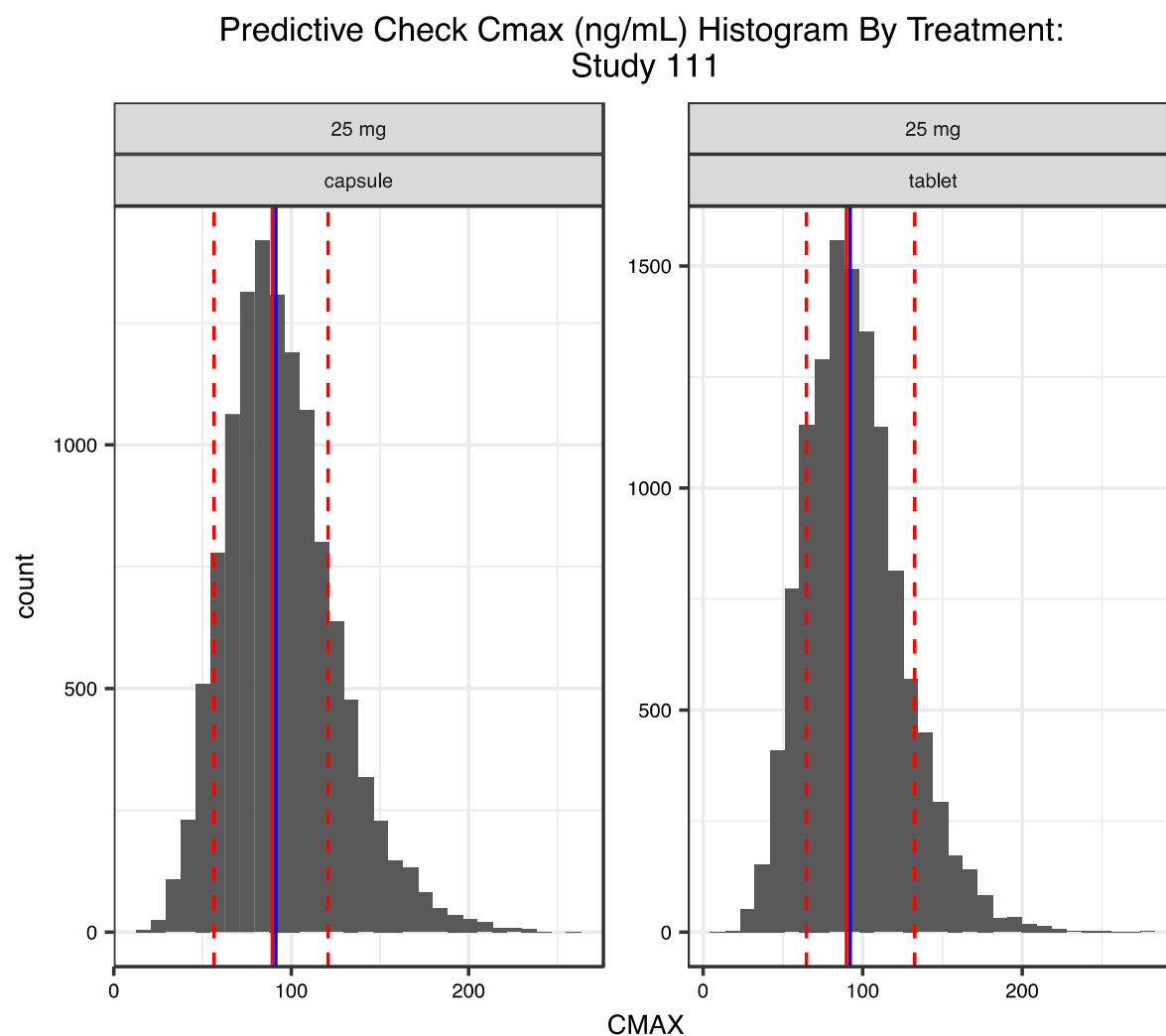
<sup>1</sup> Histograms of SEP-363856 C<sub>max</sub> values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S25. Predictive check for Study 111<sup>1</sup>.



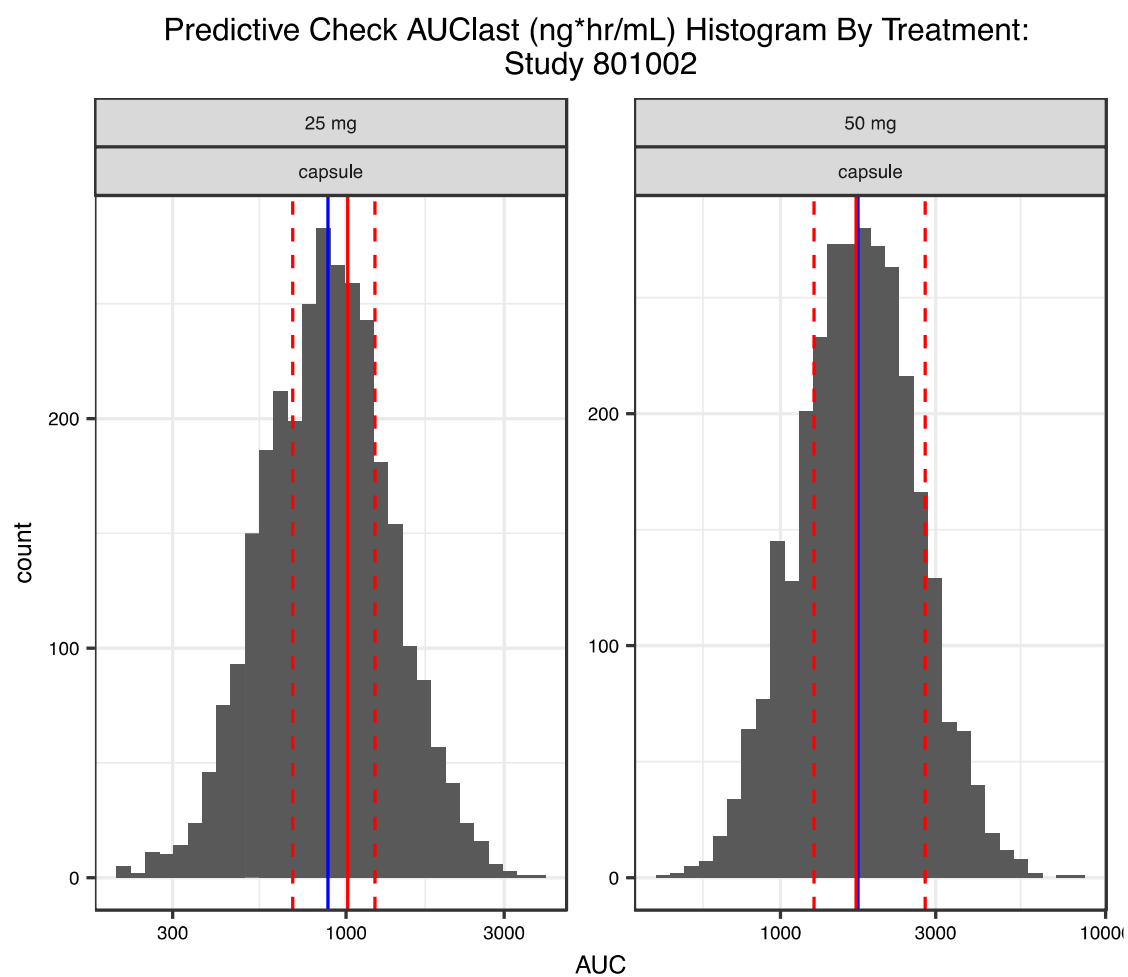
<sup>1</sup> Histograms of SEP-363856 AUC<sub>last</sub> values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S26. Predictive check for Study 111<sup>1</sup>.



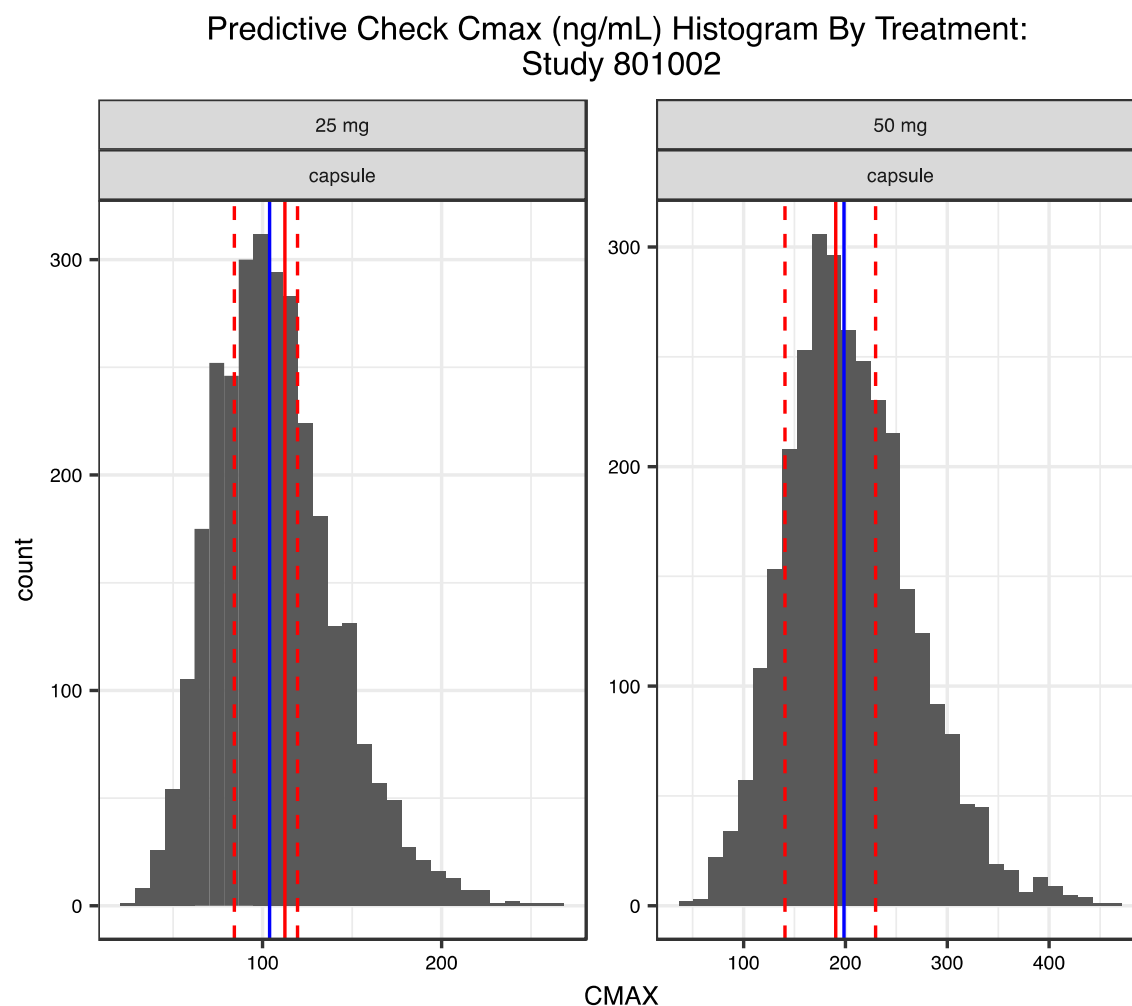
<sup>1</sup> Histograms of SEP-363856 Cmax values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S27. Predictive check for Study 801002<sup>1</sup>.



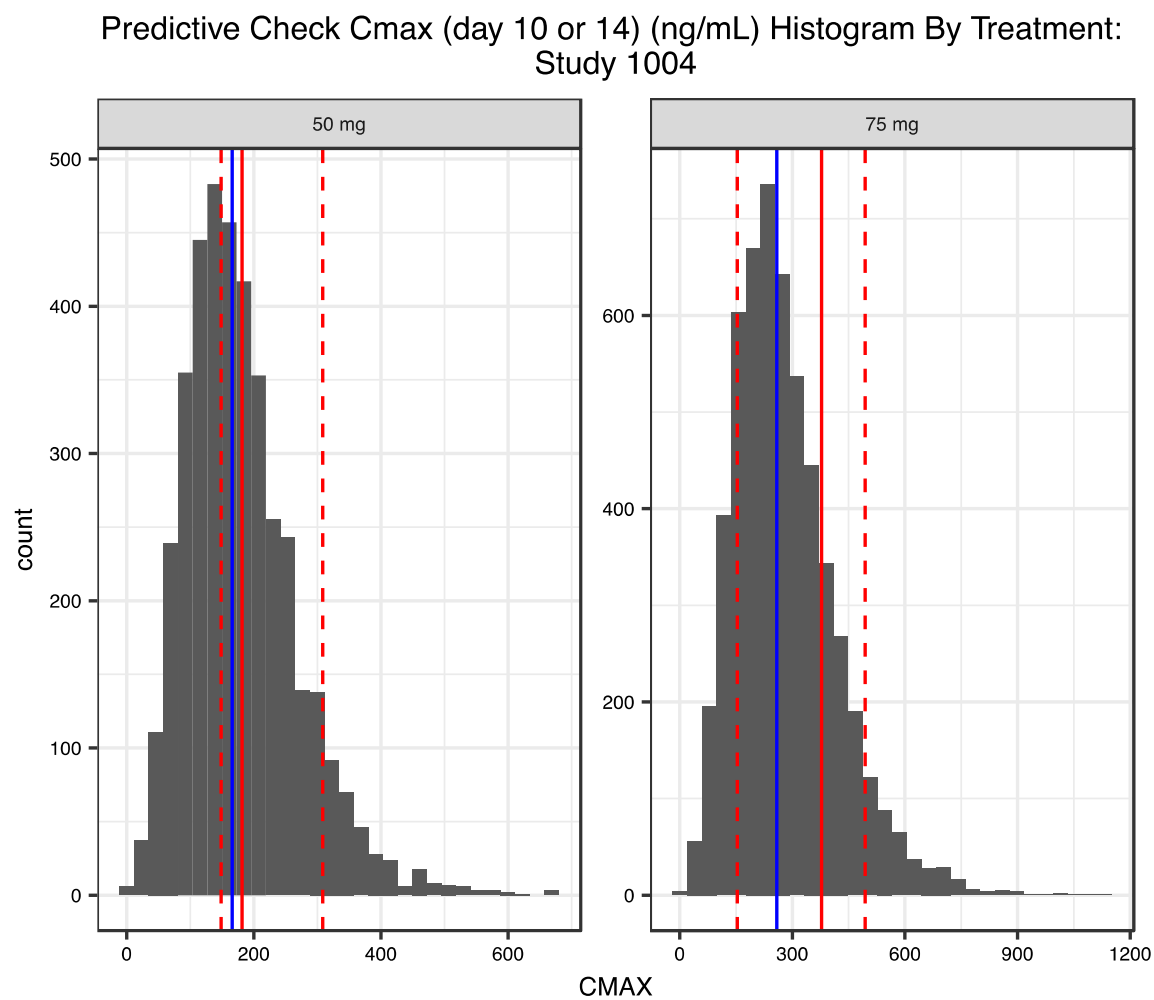
<sup>1</sup> Histograms of SEP-363856 AUClast values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S28. Predictive check for Study 801002<sup>1</sup>.



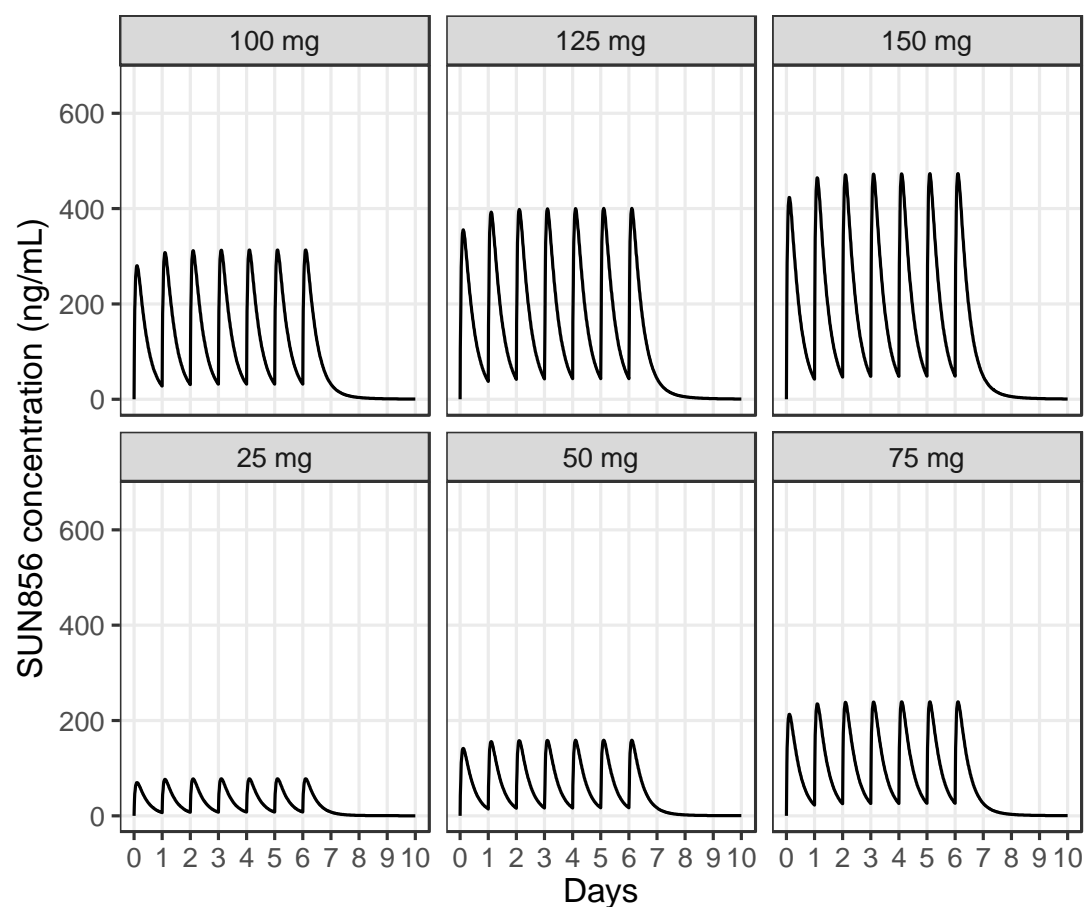
<sup>1</sup> Histograms of SEP-363856 Cmax values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

Figure S29. Predictive check for Study 1004<sup>1</sup>.



<sup>1</sup> Histograms of SEP-363856 Cmax values are shown for 500 simulation replicates from the full model. The solid blue line represents the median simulated value. The solid red and red dashed lines represent the median and 95% observed interval for the respective group and study.

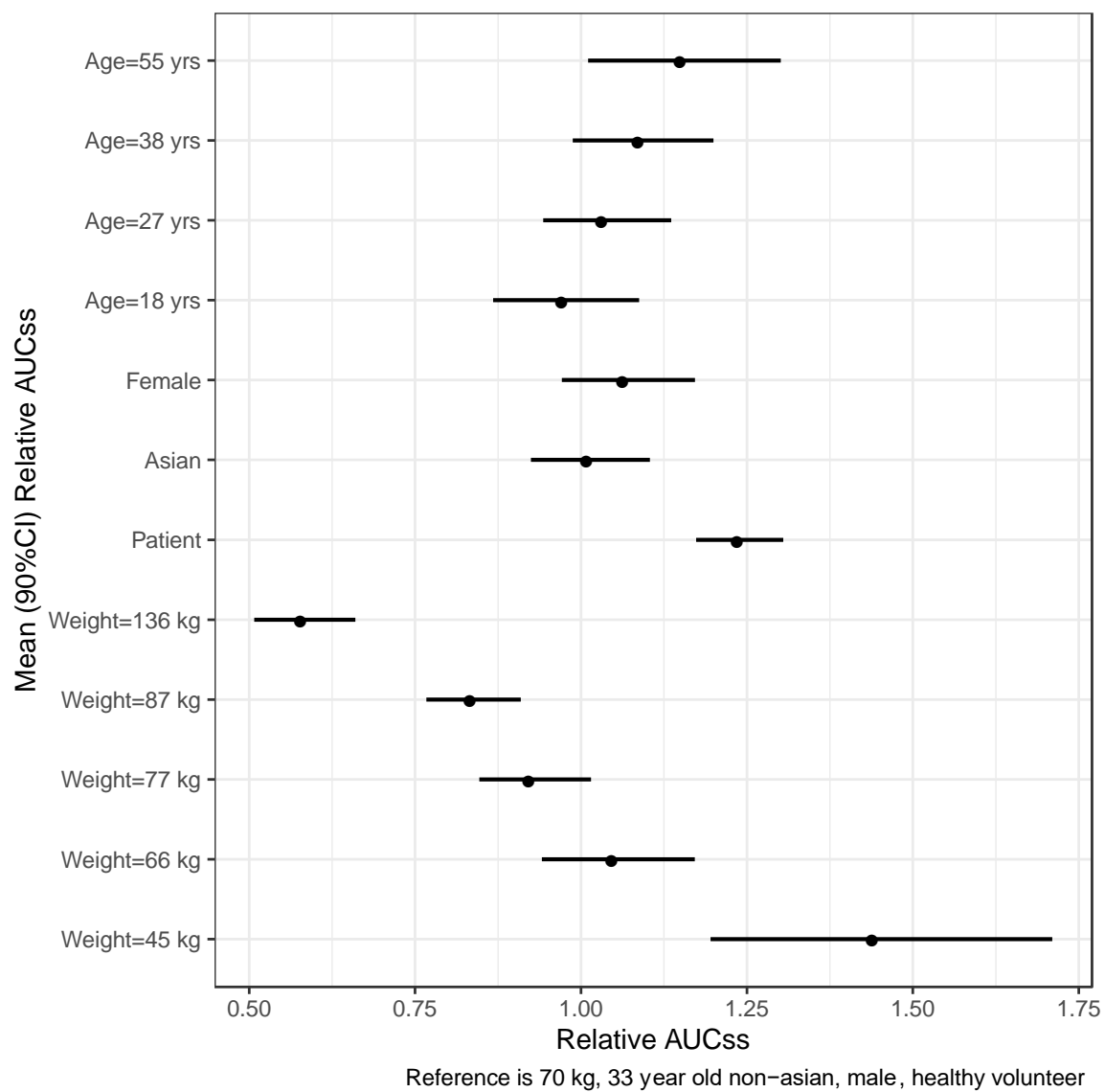
Figure S30. Typical value concentration vs. time<sup>1</sup>.



Schizophrenia patient covariates jointly resampled from studied patients .

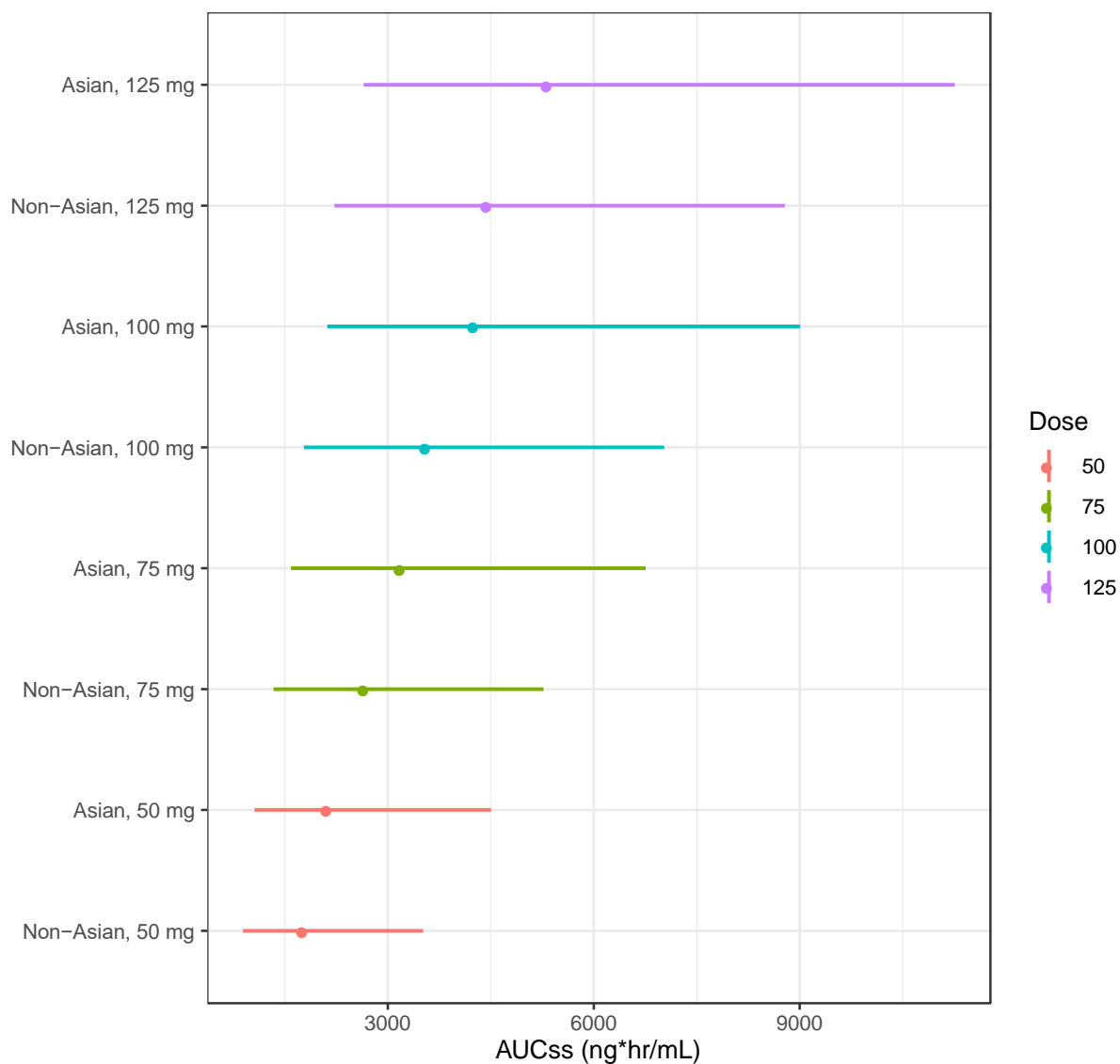
<sup>1</sup> Concentrations were simulated by resampling 1000 patients from the analysis set and simulating 7 doses at 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, and 150 mg QD. Shaded regions represent one standard deviation of the geometric mean.

Figure S31. Forest plot of effects of covariate factors on relative AUCss.



<sup>1</sup> Blue interval indicates 80-125% CI of bioequivalence criteria, points and interval lines indicate the median and 90% CI for the indicated covariate effect. AUCss was calculated assuming a 50 mg SEP-363856 dose.

Figure S32. Simulated SEP-363856 AUCss In Asian and non-Asian Patients following 50, 75, 100, or 125 mg QD dosing<sup>1</sup>.



<sup>1</sup> Points represent the median values of 1000 simulated patients and lines represent their 90% prediction interval.

## Supplemental tables

Table S1. Overview of pharmacokinetic studies

Study	Population	Design	Dose (mg)	Expected N	PK Sampling
SEP-361-101	Healthy males	Parallel group, single-blind, placebo-controlled, Ascending single dose	5, 10, 25, 50, 100, 125	Up to 88	Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hr postdose
SEP-361-103	Healthy males	Parallel group, double-blind, placebo-controlled, 2-stage, 2-way cross-over, single dose	10 or 50	24	Predose and 2, 4, 6, and 8 hr postdose
SEP-361-105	Males and females with schizophrenia	Parallel group, single-blind, placebo-controlled, ascending single dose	25, 50, 100, 150	48	Predose and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, and 144 hr postdose
SEP-361-106	Males and females with schizophrenia	Part 1: Parallel group, single-blind, placebo-controlled, multiple dose Part 2: Open-label	Part 1: 10, 25, 50, 75, 100;	45	Part 1: Predose and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hr postdose on Day 1, Predose on Day 3 to Day 6, Predose and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, and 144 hr postdose on Day 7. Part 2: Predose on Day 1 through Day 12, Predose and 0.5,

			Part 2: 75QD Day 1 to Day 28		1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hr postdose on Day 13
SEP-361-111	Healthy males and females	Open-label, crossover, single dose	25 tablet vs. capsule	24	Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hr postdose
DA801002	Healthy males	Parallel-group, placebo- controlled, single blind, Ascending single dose	25, 50	16	Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hr postdose
SEP-361- 1004	Males and females with schizophrenia	Multiple dose, open-label	Cohort 1: 25 for 3 days; 50 for 24 7 days.  Cohort 2: 50 for 3 days; 75 for 7 days.  Cohort 3: 25 for 3 days; 50 for 4 days;	24	Day 1: 2.5 hrs postdose.  Day 10: Predose, 2.5 and 7 hrs postdose  Day 11 (or 15 for Cohort 3): 24 hours after Day 10 dose.

			75 for 7 days.		
SEP-361-201	Males and females with schizophrenia	Phase 2, parallel group, double-blind, flexible dose	50, 75	240	Predose on Day 1, one postdose sample on Day 29
SEP-361-202	Males and females with schizophrenia	26-week open-label extension study following study 201	50 Week 1; 25, 50, or 75 (flex) Weeks 2-26		Predose on Days 1, 8, 29, 113, 183

Table S2. Base model parameter table<sup>20</sup>.

Parameter	Estimate	95% CI	%CV or p
$CL/F$ (L/hr)	27.2	(25.9, 28.7)	
$V_c/F$ (L)	221	(212, 229)	
$Q/F$ (L/hr)	0.774	(0.633, 0.947)	
$V_p/F$ (L)	18.3	(15.4, 21.8)	
$k_a$ (1/hr)	0.992	(0.856, 1.15)	
Weight <sub>CL</sub>	0.750	-	
Weight <sub>v</sub>	1.00	-	
$CL/F$	0.188	(0.120, 0.255)	45.5 (%CV)
$CL/F - V_c/F$	0.0458	(0.0115, 0.0801)	0.634 ( $\rho$ )
$CL/F - k_a$	-0.144	(-0.307, 0.0190)	-0.413 ( $\rho$ )
$CL/F - V_p/F$	-0.0357	(-0.102, 0.0307)	-0.201 ( $\rho$ )
$V_c/F$	0.0278	(0.0142, 0.0414)	16.8 (%CV)
$V_c/F - k_a$	-0.0151	(-0.0770, 0.0468)	-0.113 ( $\rho$ )
$V_c/F - V_p/F$	0.0267	(0.00423, 0.0491)	0.390 ( $\rho$ )
$k_a$	0.646	(0.254, 1.04)	95.2 (%CV)
$k_a - V_p/F$	0.107	(-0.0253, 0.239)	0.325 ( $\rho$ )
$V_p/F$	0.168	(0.114, 0.222)	42.8 (%CV)
Residual (proportional)	0.102	(0.0847, 0.119)	42.8 (%CV)

<sup>20</sup> The base model includes only weight as a covariate (on relative clearance and central volume) with IIV on relative clearance ( $CL/F$ ), central volume ( $V_c$ ), the absorption rate constant ( $k_a$ ), and peripheral volume ( $V_p/F$ ).

## Supplemental methods

### Predictive checks

A complete data approach was used in the predictive checks, BLQ samples were imputed with individual predictions to make a complete observed data set. Five hundred Monte Carlo simulation replicates of the original data set were generated using the full population PK model including inter-individual (IIV) and residual error. Predicted PK (VPC) or summary statistics of PK (PPC) were calculated per individual, per simulation, and the distribution of these simulated statistics was then compared to the distribution of the observed statistics. PK for the VPCs were dose normalized to ease comparison and summarized at the 5<sup>th</sup>, 50<sup>th</sup>, and 95<sup>th</sup> percentiles. Summaries included the simulated median and 95% CI for each percentile. Summary statistics of the PK in the PPCs include AUC from the beginning of dosing through the end of observation ( $AUC_{last}$ ), maximum concentration in the dosing interval ( $C_{max}$ ) in a specific dose (e.g., first or final dose in multiple dosing), minimum concentration in the dosing interval ( $C_{trough}$ ), and the continuous time-concentration curve.

### Typical value simulations

Using parameter estimates from the fu model, simulations were performed to describe the typical concentration time curve for schizophrenia patients at doses of 25, 50, 75, 100, 125, and 150 mg once daily (QD). These typical value simulations were calculated as a mean trajectory from patient covariate settings re-sampled from the analysis set. For each of 1000 re-sampled patients with schizophrenia, concentration-time profiles were simulated including IIV and residual error (but not parameter uncertainty) for 10 days at 15-minute intervals under a 7-day QD dosing regimen. The typical value profile was then calculated using the geometric mean of the 1000 re-sampled patients at each time point and with plus and minus one standard deviation of the geometric mean.